Substituted lactams and their use as anti-cancer agents

The present invention relates to the area of therapeutic agents for the treatment of cancer. More particularly, the present invention relates to certain substituted lactams, pharmaceutical compositions comprising said lactam compounds, a method of treating cancer with said lactam compounds, and a process for preparing said lactam compounds.

BACKGROUND

Cancer is a serious health problem throughout the world. As a result, an extensive number of research endeavors has been undertaken in an effort to develop therapies appropriate to the treatment and alleviation of cancer in humans. Research has been conducted to develop anti-cancer agents effective against various types of cancer. Oftentimes, anti-cancer agents which have been developed and found effective against cancer cells are, unfortunately, also toxic to normal cells. This toxicity manifests itself in weight loss, nausea, vomiting, hair loss, fatigue, itching, hallucinations, loss of appetite, and other undesirable effects.

Additionally, conventionally used cancer treatment agent often do not have the effectiveness desired or are not as broadly effective against different types of cancers as desired. As a result, a great need exists for therapeutic agents which are not only more effective against multiple types of cancer, but which have a higher degree of selectivity for killing cancer cells with no or minimal effect on normal healthy cells. In addition, highly effective and selective anti-cancer agents, in particular, against cancers of the colon, bladder, prostate, stomach, pancreas, breast, lung, liver, brain, testis, ovary, cervix, skin, vulva, small intestine, lymph glands, and blood cells are desired. Moreover, anti-cancer activity against colon, breast, lung, pancreas, and prostate cancers as well as melanomas are particularly desired because of the lack of any particular effective therapy at the present time.

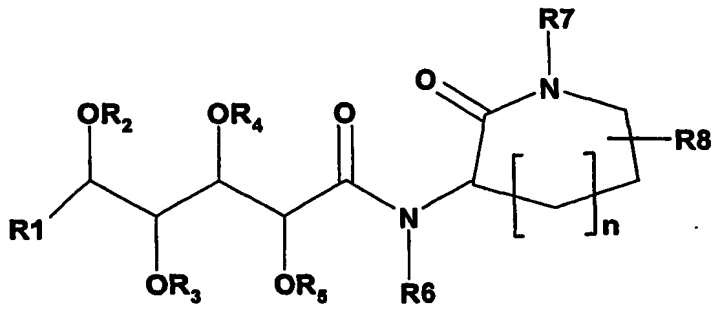
SUMMARY

The present invention provides new anti-cancer agents which are effective against a variety of cancer cells in particular, against all liquid and solid cancers that may arise in a subject, including cancers of the colon, bladder, prostate, stomach, pancreas, breast, lung, liver,

brain, testis, ovary, cervix, skin, vulva, small intestine, lymph glands, and blood cells. More particularly, the present invention relates to certain substituted lactams which exhibit a high degree of selectivity in killing cancer cells.

DETAILED DESCRIPTION

The invention relates to pharmaceutical compounds that are useful for the treatment of cancer of the formula I:



(I)

wherein

n is 0, 1 or 2;

R1 is H, X_1-(C_{1-6}) alkyl-, (C_{1-12})alkylC(O)-, X_2-(C_{2-4}) alkenylene-, X_2-(C_{2-4}) alkynylene-, X_1-(C_{3-9})cycloalkyl-, X_2-(C_{3-9})cycloalkene-, X_1-aryl-, X_1-(C_{3-7})cycloalkane-(C_{1-6})alkylene-, X_2-(C_{3-7})cycloalkene-(C_{1-6})alkylene-, or X_1-aryl-(C_{1-6})alkylene-;

X_1 is H, (C_{1-14})alkyl, (C_{3-7})cycloalkyl, (C_{1-14})alkyl substituted by (C_{3-7})cycloalkyl, -OR_a, -SR_a, -NO_2, halo or (C_{1-6})alkylC(O)-; aryl, aryl-(C_{1-12})alkyl-, -OR_a, -SR_a, -NO_2, halo, (C_{1-12})alkyl-C(O)-, mono- or di-(C_{1-4})alkylamino, amino(C_{1-16})alkyl-, or mono- or di-(C_{1-4})alkylamino(C_{1-16})alkyl;

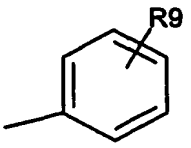
X_2 is H, (C_{1-14})alkyl, (C_{3-7})cycloalkyl, (C_{1-14})alkyl substituted by (C_{3-7})cycloalkyl, -OR_a -SR_a, -NO_2, halo or (C_{1-6})alkyl-C(O)-; aryl, aryl-(C_{1-12})alkyl-, amino(C_{1-16})alkyl- or mono- or di-(C_{1-4})alkylamino(C_{1-16})alkyl;

R_a is H, (C_{1-18})alkyl, aryl, or (C_{1-18})alkyl substituted by (C_{3-7})cycloalkyl, aryl, -OH, -O-(C_{1-6})alkyl or halo;

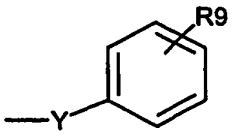
R_2, R_3, R_4 and R_5 are independently hydrogen or (C_{1-18})alkyl, R_5 is also phenyl or (C_{1-18})alkyl which is substituted by phenyl, wherein there is no more than a total of 18 carbon atoms in the combined R_2, R_3, R_4 and R_5 alkyl substituents, or R_2 and R_4 together or R_3 and R_5 together form an acetal group;

R6 is hydrogen or (C_{1-6}) alkyl;

R7 is H, (C_{1-18})alkyl, phenyl, pyridyl, (C_{1-18})alkyl substituted by (C_{3-7})cycloalkyl, $-OR_x$, N_3, halo, -$N(R_x)_2$, R_x, -O-(C_{1-6})alkyl, -OC(O)-(C_{1-16})alkyl or pyridyl; -Y-R_b or a substituent of formula IIa or IIIa



IIa



IIIa

wherein

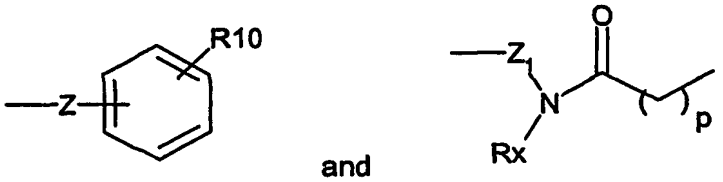
R9 is from 0 to 3 substituents selected from (C_{1-6})alkyl, -OR_a, -SR_a, -NO_2, halo, -N_3, (C_{1-12})alkylC(O)-, mono- or di-(C_{1-4})alkylamino, amino(C_{1-16})alkyl-, mono- or di-(C_{1-4})alkylamino(C_{1-16})alkyl, $(CH_2)_{0-2}$-C_{5-7}cycloalkyl, $(CH_2)_{0-2}$-heterocyclic, $(CH_2)_{0-2}$-C_{5-7}aryl, or $(CH_2)_{0-2}$-heteroaryl;

Y is a linking group selected from -(C_{1-10})alkyl-, -(C_{0-10})alkylene-CO-N(R_x)-(C_{0-10})alkylene-, -(C_{0-10})alkylene-N(R_x)-CO-(C_{0-10})alkylene-, -(C_{0-10})alkylene-CO-O-(C_{0-10})alkylene-, -(C_{1-10})alkylene-O-C(O)-(C_{1-10})alkylene-, -(C_{0-10})alkylene-CO-(C_{0-10})alkylene-, -(C_{0-10})alkylene-(R_x)N-CO-O-(C_{0-10})alkylene-, -(C_{0-10})alkylene-O-CO-(R_x)N-(C_{0-10})alkylene- or -(C_{0-18})alkylene-arylene-(C_{0-18})alkylene-;

R_x is H, (C_{1-4})alkyl or phenyl;

R_b is (C_{1-16})alkyl or (C_{1-16})alkyl which is substituted by (C_{3-7})cycloalkyl, $-OR_x$, N_3, halo, $-N(R_x)_2$, $-O-(C_{1-8})$alkyl, $-OC(O)-(C_{1-16})$alkyl or pyridyl;

R8 is H, halo, $-N_3$, (C_{1-16})alkyl, $-Z-(C_{1-16})$alkyl, (C_{1-16})alkyl substituted by (C_{3-7})cycloalkyl, $-N_3$, $-N(R_x)_2$, -Z-het, $-OR_a$ or $-SR_a$, $-Z-(C_{1-16})$alkyl substituted by (C_{3-7})cycloalkyl, $-N_3$, $-N(R_x)_2$, -Z-het, $-OR_a$ or $-SR_a$, $-O(C_{1-16})$alkylene-N_3, $-O(C_{1-16})$alkylene-$N(R_x)_2$, $-(C_{0-8})$alkylene-$OC(O)-(C_{1-16})$alkyl, $-(C_{0-8})$alkylene-$(O)C-O-(C_{1-16})$alkyl, $-(C_{0-8})$alkylene-$OC(O)-(C_{3-7})$cycloalkyl, $-(C_{0-8})$alkylene-$(O)C-O-(C_{3-7})$cycloalkyl, pyridyl, $-OC(O)O(C_{1-12})$alkyl, $-O-CO-X-R_z$, or $-O-CO-(CH_2)_m-O-(CH_2)_m-X-R_z$ wherein X is a direct bond, (C_{1-12})alkylene, (C_{1-12})alkenylene or (C_{1-12})alkynylene and R_z is H, (C_{3-9})cycloalkyl, phenyl, phenyl substituted by one or more of chloro, methoxy, (C_{1-16})alkyl or (C_{1-16})alkoxy, pyrrolyl, furanyl, thiofuranyl, indolyl, benzofuranyl, benzothiofuranyl or pyridyl and each m is independently a number from 0 to 13, -Z-het, $-OR_a$, $-SR_a$, mono- or di-(C_{1-4})alkylamino, amino(C_{1-16})alkyl-, mono- or di-(C_{1-4})alkylamino(C_{1-16})alkyl, $-Z-Si((C_{1-8})alkyl)_3$ or a substituent selected from the following two formulae:



Z is a direct bond, $-(C_{1-12})$alkylene-, $-(C_{1-12})$alkylene-O-, $-O-(C_{1-12})$alkylene-, $-(C_{1-12})$alkylene-$N(R_x)$-, $-N(R_x)$-, $-N(R_x)-(C_{1-12})$alkylene-, $-N(R_x)-C(O)$-, $-N(R_x)-C(O)-(C_{1-12})$alkylene-, $-(C_{1-12})$alkylene-$N(R_x)-C(O)$-, $-(C_{1-8})$alkylene-$N(R_x)-C(O)-(C_{1-8})$alkylene-, $-(C_{1-12})$alkylene-$CO-N(R_x)$-, $-CO-N(R_x)-(C_{1-12})$alkylene-, $-(C_{1-8})$alkylene-$CO-N(R_x)-(C_{1-8})$alkylene-, $-CO-N(R_x)$-, $-(C_{1-12})$alkylene-CO-O-, $-(C_{1-12})$alkylene-$O-C(O)$-, $-OC(O)-(C_{1-12})$alkylene-, $-C(O)-O-(C_{1-12})$alkylene-, $-(C_{1-12})$alkylene-CO-, $-(C_{1-8})$alkylene-$CO-(C_{1-8})$alkylene-, $-CO-(C_{1-12})$alkylene-, -C(O)-, $-N(R_x)-C(O)-O$-, $-N(R_x)-C(O)-O-(C_{1-12})$alkylene-, $-(C_{1-12})$alkylene-$N(R_x)-C(O)-O$-, $-(C_{1-8})$alkylene-$N(R_x)-C(O)-O-(C_{1-8})$alkylene-, $-(C_{1-12})$alkylene-$O-CO-N(R_x)$-, $-O-CO-N(R_x)-(C_{1-12})$alkylene-, $-(C_{1-8})$alkylene-$O-CO-N(R_x)-(C_{1-8})$alkylene-, $-O-CO-N(R_x)$-, -O-CO-O-, $-(C_{1-12})$alkylene-O-CO-O-, -O-CO-O-(C_{1-12})alkylene- or $-(C_{1-8})$alkylene-$O-C(O)-O-(C_{1-8})$alkylene-;

Z_1 is a direct bond, $-(C_{1-12})$alkylene-, $-O-(C_{1-12})$alkylene-, $-N(R_x)-(C_{1-12})$alkylene-, $-N(R_x)-C(O)-(C_{1-12})$alkylene-, $-(C_{1-8})$alkylene-$N(R_x)-C(O)-(C_{1-8})$alkylene-, $-CO-N(R_x)-(C_{1-12})$alkylene-, $-(C_{1-8})$alkylene-$CO-N(R_x)-(C_{1-8})$alkylene-, $-OC(O)-(C_{1-12})$alkylene-, $-C(O)-O-(C_{1-12})$alkylene-, $-(C_{1-}$

$_8$)alkylene-CO-(C_{1-8})alkylene-, -CO-(C_{1-12})alkylene-, -C(O)-, -N(R_x)-C(O)-O-(C_{1-12})alkylene-, -(C_{1-8})alkylene-N(R_x)-C(O)-O-(C_{1-8})alkylene-, -O-CO-N(R_x)-(C_{1-12})alkylene-, -(C_{1-8})alkylene-O-CO-N(R_x)-(C_{1-8})alkylene-, -O-CO-O-(C_{1-12})alkylene- or -(C_{1-8})alkylene-O-C(O)-O-(C_{1-8})alkylene-;

R10 is from 0 to 3 substituents selected from hydroxy, halo, -(C_{1-17})alkyl, -O-(C_{1-17})alkyl, -$(CH_2)_{1-6}$-C_{3-7}-cycloalkyl, -$(CH_2)_{0-10}$-aryl or -$(CH_2)_{0-10}$ –het;

het is a heterocyclic or heteroaromatic ring;

p is 1-18;
or a pharmaceutically acceptable salt thereof;
with the proviso that when n is 2 and R_1 is (C_{1-6})alkyl-CH=CH- or (C_{3-6})cycloalkyl-CH=CH- then R_7 is not H or (C_{1-8})alkyl or R_8 is not –O-CO-X-R_Z or –O-CO-$(CH_2)_m$-O-$(CH_2)_m$-X-R_Z where X is a direct bond, (C_{1-12})alkylene, (C_{1-12})alkenylene or (C_{1-12})alkynylene and R_z is H, (C_{3-9})cycloalkyl, phenyl, phenyl substituted by one or more of chloro, methoxy, (C_{1-18})alkyl or (C_{1-18})alkoxy, pyrrolyl, furanyl, thiofuranyl, indolyl, benzofuranyl, benzothiofuranyl or pyridyl and each m is independently a number from 0 to 13, and with the further proviso that R_8 is not –OH when n is 2, R_7 is H or methyl and R_1 is 3-methylbut-1-enylene.

The present invention further also relates to compounds that are useful for the treatment of cancer of the formula I, wherein

n is 0, 1 or 2;

R1 is X_1-(C_{1-6}) alkyl-, X_2-(C_{2-4}) alkenylene-, X_2-(C_{2-4}) alkynylene-, X_1-(C_{3-9})cycloalkyl-, X_2-(C_{3-9})cycloalkene-, X_1-aryl-, X_1-(C_{3-7})cycloalkane-(C_{1-6})alkylene-, X_2-(C_{3-7})cycloalkene-(C_{1-6})alkylene-, or X_1-aryl-(C_{1-6})alkylene-;

X_1 is H, (C_{1-14})alkyl, (C_{3-7})cycloalkyl, (C_{1-14})alkyl substituted by (C_{3-7})cycloalkyl, -OR_a, -SR_a, -NO_2, halo or (C_{1-6})alkylC(O)-; aryl, aryl-(C_{1-12})alkyl-, -OR_a, -SR_a, -NO_2, halo, (C_{1-12})alkyl-C(O)-, mono- or di-(C_{1-4})alkylamino, amino(C_{1-16})alkyl-, or mono- or di-(C_{1-4})alkylamino(C_{1-16})alkyl;

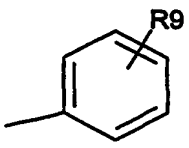
X_2 is H, (C_{1-14})alkyl, (C_{3-7})cycloalkyl, (C_{1-14})alkyl substituted by (C_{3-7})cycloalkyl, $-OR_a$ $-SR_a$, $-NO_2$, halo or (C_{1-8})alkyl-C(O)-; aryl, aryl-(C_{1-12})alkyl-, amino(C_{1-16})alkyl- or mono- or di-(C_{1-4})alkylamino(C_{1-16})alkyl;

R_a is H, (C_{1-18})alkyl, aryl, or (C_{1-18})alkyl substituted by (C_{3-7})cycloalkyl, aryl, -OH, -O-(C_{1-8})alkyl or halo;

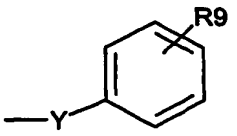
R_2, R_3, R_4 and R_5 are independently hydrogen or (C_{1-18})alkyl, R_5 is also phenyl or (C_{1-16})alkyl which is substituted by phenyl, wherein there is no more than a total of 18 carbon atoms in the combined R_2, R_3, R_4 and R_5 alkyl substituents, or R_2 and R_4 together or R_3 and R_5 together form an acetal group;

R6 is hydrogen or (C_{1-8}) alkyl;

R7 is H, (C_{1-18})alkyl, phenyl, pyridyl, (C_{1-18})alkyl substituted by (C_{3-7})cycloalkyl, $-OR_x$, N_3, halo, $-N(R_x)_2$, -O-(C_{1-8})alkyl, -OC(O)-(C_{1-16})alkyl or pyridyl; -Y-R_b or a substituent of formula IIa or IIIa



IIa



IIIa

wherein

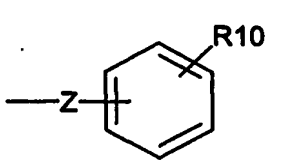
R9 is from 0 to 3 substituents selected from (C_{1-8})alkyl, $-OR_a$, $-SR_a$, $-NO_2$, halo, $-N_3$, (C_{1-12})alkylC(O)-, mono- or di-(C_{1-4})alkylamino, amino(C_{1-16})alkyl-, or mono- or di-(C_{1-4})alkylamino(C_{1-16})alkyl;

Y is a linking group selected from -(C_{1-10})alkyl-, -(C_{0-10})alkylene-CO-N(R_x)-(C_{0-10})alkylene-, -(C_{0-10})alkylene-N(R_x)-CO-(C_{0-10})alkylene-, -(C_{0-10})alkylene-CO-O-(C_{0-10})alkylene-, -(C_{1-10})alkylene-O-C(O)-(C_{1-10})alkylene-, -(C_{0-10})alkylene-CO-(C_{0-10})alkylene-, -(C_{0-10})alkylene-(R_x)N-CO-O-(C_{0-10})alkylene-, -(C_{0-10})alkylene-O-CO-(R_x)N-(C_{0-10})alkylene- or -(C_{0-18})alkylene-arylene-(C_{0-18})alkylene-;

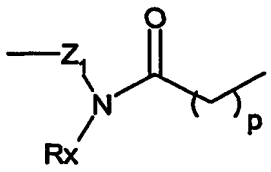
R_x is H, (C_{1-4})alkyl or phenyl;

R_b is (C_{1-16})alkyl or (C_{1-16})alkyl which is substituted by (C_{3-7})cycloalkyl, $-OR_x$, N_3, halo, $-N(R_x)_2$, -O-(C_{1-6})alkyl, -OC(O)-(C_{1-16})alkyl or pyridyl;

R8 is H, halo, $-N_3$, (C_{1-16})alkyl, -Z-(C_{1-16})alkyl, (C_{1-16})alkyl substituted by (C_{3-7})cycloalkyl, $-N_3$, $-N(R_x)_2$, -Z-het, $-OR_a$ or $-SR_a$, -Z-(C_{1-16})alkyl substituted by (C_{3-7})cycloalkyl, $-N_3$, $-N(R_x)_2$, -Z-het, $-OR_a$ or $-SR_a$, -O(C_{1-16})alkylene-N_3, -O(C_{1-16})alkylene-$N(R_x)_2$, -(C_{0-6})alkylene-OC(O)-(C_{1-16})alkyl, -(C_{0-6})alkylene-(O)C-O-(C_{1-16})alkyl, -(C_{0-6})alkylene-OC(O)-(C_{3-7})cycloalkyl, -(C_{0-6})alkylene-(O)C-O-(C_{3-7})cycloalkyl, pyridyl, -OC(O)O(C_{1-12})alkyl, -Z-het, $-OR_a$, $-SR_a$, mono- or di-(C_{1-4})alkylamino, amino(C_{1-16})alkyl-, mono- or di-(C_{1-4})alkylamino(C_{1-16})alkyl, -Z-Si((C_{1-6})alkyl)$_3$ or a substituent selected from the following two formulae:



and



Z is a direct bond, -(C_{1-12})alkylene-, -(C_{1-12})alkylene-O-, -O-(C_{1-12})alkylene-, -(C_{1-12})alkylene-$N(R_x)$-, $-N(R_x)$-, $-N(R_x)$-(C_{1-12})alkylene-, $-N(R_x)$-C(O)-, $-N(R_x)$-C(O)-(C_{1-12})alkylene-, -(C_{1-12})alkylene-$N(R_x)$-C(O)-, -(C_{1-8})alkylene-$N(R_x)$-C(O)-(C_{1-8})alkylene-, -(C_{1-12})alkylene-CO-$N(R_x)$-, -CO-$N(R_x)$-(C_{1-12})alkylene-, -(C_{1-8})alkylene-CO-$N(R_x)$-(C_{1-8})alkylene-, -CO-$N(R_x)$-, -(C_{1-12})alkylene-CO-O-, -(C_{1-12})alkylene-O-C(O)-, -OC(O)-(C_{1-12})alkylene-, -C(O)-O-(C_{1-12})alkylene-, -(C_{1-12})alkylene-CO-, -(C_{1-8})alkylene-CO-(C_{1-8})alkylene-, -CO-(C_{1-12})alkylene-, -C(O)-, $-N(R_x)$-C(O)-O-, $-N(R_x)$-C(O)-O-(C_{1-12})alkylene-, -(C_{1-12})alkylene-$N(R_x)$-C(O)-O-, -(C_{1-8})alkylene-$N(R_x)$-C(O)-O-(C_{1-8})alkylene-, -(C_{1-12})alkylene-O-CO-$N(R_x)$-, -O-CO-$N(R_x)$-(C_{1-12})alkylene-, -(C_{1-8})alkylene-O-CO-$N(R_x)$-(C_{1-8})alkylene-, -O-CO-$N(R_x)$-, -O-CO-O-, -(C_{1-12})alkylene-O-CO-O-, -O-CO-O-(C_{1-12})alkylene- or -(C_{1-8})alkylene-O-C(O)-O-(C_{1-8})alkylene-;

Z_1 is a direct bond, -(C_{1-12})alkylene-, -O-(C_{1-12})alkylene-, $-N(R_x)$-(C_{1-12})alkylene-, $-N(R_x)$-C(O)-(C_{1-12})alkylene-, -(C_{1-8})alkylene-$N(R_x)$-C(O)-(C_{1-8})alkylene-, -CO-$N(R_x)$-(C_{1-12})alkylene-, -(C_{1-8})alkylene-CO-$N(R_x)$-(C_{1-8})alkylene-, -OC(O)-(C_{1-12})alkylene-, -C(O)-O-(C_{1-12})alkylene-, -(C_{1-8})alkylene-CO-(C_{1-8})alkylene-, -CO-(C_{1-12})alkylene-, -C(O)-, $-N(R_x)$-C(O)-O-(C_{1-12})alkylene-, -(C_{1-8})alkylene-$N(R_x)$-C(O)-O-(C_{1-8})alkylene-, -O-CO-$N(R_x)$-(C_{1-12})alkylene-, -(C_{1-8})alkylene-

O-CO-N(R_x)-(C_{1-8})alkylene-, -O-CO-O-(C_{1-12})alkylene- or -(C_{1-8})alkylene-O-C(O)-O-(C_{1-8})alkylene-;

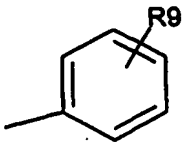
R10 is from 0 to 3 substituents selected from hydroxy, halo, -(C_{1-17})alkyl, -O-(C_{1-17})alkyl, -$(CH_2)_{1-8}$-C_{3-7}-cycloalkyl, -$(CH_2)_{0-10}$-aryl or -$(CH_2)_{0-10}$ –het;

het is a heterocyclic or heteroaromatic ring;

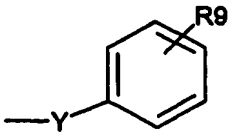
p is 1-18;
or a pharmaceutically acceptable salt thereof;
with the proviso that when n is 2 and R_1 is (C_{1-8})alkyl-CH=CH- or (C_{3-8})cycloalkyl-CH=CH- then R_7 is not H or (C_{1-8})alkyl or R_8 is not –O-CO-X-R_Z or –O-CO-$(CH_2)_m$-O-$(CH_2)_m$-X-R_Z where X is a direct bond, (C_{1-12})alkylene, (C_{1-12})alkenylene or (C_{1-12})alkynylene and R_z is H, (C_{3-9})cycloalkyl, phenyl, phenyl substituted by one or more of chloro, methoxy, (C_{1-18})alkyl or (C_{1-18})alkoxy, pyrrolyl, furanyl, thiofuranyl, indolyl, benzofuranyl, benzothiofuranyl or pyridyl and each m is independently a number from 0 to 13, and with the further proviso that R_8 is not –OH when n is 2, R_7 is H or methyl and R_1 is 3-methylbut-1-enylene.

Interesting compounds of formula I are those wherein:
n is 2; and/or
R1 is X_1-(C_{1-8}) alkyl-, X_2-(C_{2-4}) alkenylene-, X_1-(C_{3-7})cycloalkyl-, or X_1-(C_{3-7})cycloalkane-(C_{1-3})alkylene-; and/or
X_1 is H, (C_{1-12})alkyl, especially branched (C_{1-8})alkyl; (C_{3-7})cycloalkyl, -(C_{1-12})alkyl substituted by (C_{3-7})cycloalkyl, -OR_a; -SR_a, -NO_2, halo or (C_{1-12})alkylC(O)-; aryl, aryl-(C_{1-12})alkyl- or -OR_a; and/or
X_2 is H, (C_{1-12})alkyl, (C_{3-7})cycloalkyl, -(C_{1-12})alkyl substituted by (C_{3-7})cycloalkyl, -OR_a, -SR_a, -NO_2, halo or (C_{1-12})alkylC(O)-, aryl, aryl-(C_{1-12})alkyl-; and/or
R_a is H, (C_{1-18})alkyl, aryl-, or (C_{1-18})alkyl substituted by (C_{3-7})cycloalkyl or aryl;
R_2, R_3, R_4 and R_5 are independently hydrogen or (C_{1-4})alkyl, wherein there is no more than a total of 8 carbon atoms, especially no more than 4 carbon atoms, in the combined R_2, R_3, R_4 and R_5 alkyl substituents; and/or
R6 is hydrogen or (C_{1-6}) alkyl; and/or

R7 is H, (C_{1-8})alkyl, R_x, (C_{1-18})alkyl substituted by (C_{3-7})cycloalkyl, $-OR_x$, N_3, halo, $-N(R_x)_2$, $-O-(C_{1-8})$alkyl, $-OC(O)-(C_{1-16})$alkyl or pyridyl; especially 3-pyridyl, or a substituent of formula IIa or IIIa



IIa



IIIa

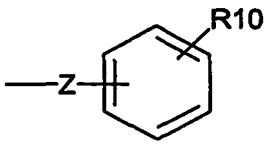
and/or

R9 is from 0 to 3 substituents selected from (C_{1-8})alkyl, $-OR_a$, $-SR_a$, $-NO_2$, halo, or $-N_3$; and/or

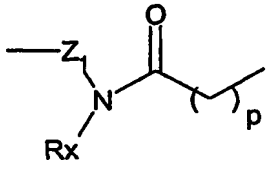
Y is a linking group selected from $-C(O)N(R_x)-$, $-CO-O-$, $-(C_{1-12})$alkylene-CO-O-, $-CO-O-(C_{1-12})$alkylene-, $-(C_{1-10})$alkylene-CO-O-(C_{1-10})alkylene-, $-(C_{1-10})$alkylene-O-C(O)-(C_{1-10})alkylene-, $-CO-$, $-(C_{1-12})$alkylene-CO-, $-CO-(C_{1-12})$alkylene-, $-(C_{1-10})$alkylene-CO-(C_{1-10})alkylene-, $-(C_{1-12})$alkylene-$(R_x)N-CO-$, $-(C_{1-10})$alkylene-$(R_x)N-CO-O-(C_{1-10})$alkylene-, or $-(C_{0-12})$alkylene-arylene-(C_{0-12})alkylene-; and/or

R_x is H, (C_{1-4})alkyl or phenyl;

R8 is $-N_3$, (C_{1-16})alkyl, -Z-(C_{1-16})alkyl, (C_{1-16})alkyl substituted by (C_{3-7})cycloalkyl, $-N_3$, or $-N(R_x)_2$; -Z-(C_{1-16})alkyl substituted in the alkyl portion by (C_{3-7})cycloalkyl, $-N_3$, or $-N(R_x)_2$, $-(C_{0-6})$alkylene-(O)C-O-(C_{1-16})alkyl, or a substituent selected from the following two formulae:



or



and/or

Z is a direct bond, $-(C_{1-12})$alkylene-, $-N(R_x)-C(O)-$, $-N(R_x)-C(O)-(C_{1-12})$alkylene-, $-(C_{1-12})$alkylene-$N(R_x)-C(O)-$, $-(C_{1-8})$alkylene-$N(R_x)-C(O)-(C_{1-8})$alkylene-, $-(C_{1-12})$alkylene-CO-$N(R_x)-$, $-CO-N(R_x)-(C_{1-12})$alkylene-, $-(C_{1-8})$alkylene-CO-$N(R_x)-(C_{1-8})$alkylene-, $-CO-N(R_x)-$, $-C(O)-O-(C_{1-12})$alkylene-, $-CO-(C_{1-12})$alkylene-, $-C(O)-$, $-N(R_x)-C(O)-O-$, $-N(R_x)-C(O)-O-(C_{1-12})$alkylene-, $-(C_{1-12})$alkylene-$N(R_x)-C(O)-O-$, $-(C_{1-8})$alkylene-$N(R_x)-C(O)-O-(C_{1-8})$alkylene-, $-(C_{1-12})$alkylene-$O-CO-N(R_x)-$, $-O-CO-N(R_x)-(C_{1-12})$alkylene-, $-(C_{1-8})$alkylene-$O-CO-N(R_x)-(C_{1-8})$alkylene- or $-O-CO-N(R_x)-$; and/or

Z_1 is a direct bond, $-(C_{1-12})$alkylene- or $-C(O)-$; and/or

R10 is from zero to 3 substituents selected from hydroxy, halo, -(C_{1-17})alkyl, -O-(C_{1-17})alkyl, -$(CH_2)_{1-6}$-C_{3-7} -cycloalkyl, -$(CH_2)_{0-10}$-aryl or -$(CH_2)_{0-10}$ –het; and/or
het is pyridyl.

Further interesting compounds of formula (I) include those wherein
R1 is (C_{1-6} alkyl)-ethenylene-; especially those wherein the alkyl group is branched and the double bond is trans; and/or
R_2, R_3 and R_4, independently are hydrogen or (C_{1-4}) alkyl, wherein there is no more than a total of 4 carbon atoms in the combined R_2, R_3, R_4 and R_5 alkyl substituents; and/or
R_5 is (C_{1-4})alkyl, especially methyl, and/or
R6 is hydrogen or methyl; and/or
R7 is H or (C_{1-6})alkyl; and/or
R8 is H, -N_3, (C_{1-16})alkyl, -Z-(C_{1-16})alkyl, (C_{1-16})alkyl substituted by (C_{3-7})cycloalkyl, -N_3, or -$N(R_x)_2$ or -Z-(C_{1-16})alkyl substituted in the alkyl portion by (C_{3-7})cycloalkyl, -N_3, or -$N(R_x)_2$,
R9 is $(CH_2)_{0-2}$-C_{5-7} cycloalkyl, $(CH_2)_{0-2}$-C_{5-7} hetero-cyclic, $(CH_2)_{0-2}$-C_{5-7} aryl, or $(CH_2)_{0-2}$-C_{5-7} hetero-aryl;
X is (C_{1-12}) alkylene or (C_{2-12}) alkenylene; and/or
R10 is from 0 to 3 substituents selected from hydroxy, halo, -(C_{1-8})alkyl, -O-(C_{1-8})alkyl, -$(CH_2)_{1-6}$-C_{3-7} -cycloalkyl, -$(CH_2)_{0-10}$-aryl or -$(CH_2)_{0-10}$ –het; and/or
het is pyridyl;
especially those wherein n is 2.

Additional interesting compounds are those of formula I where
R1 is –CH=CH-*i*-propyl or –CH=CH-*t*-butyl, especially in the trans geometry;
X_2 is H;
R_2, R_3, R_4, and R_5 independently are hydrogen or methyl;
R6 is hydrogen;
R7 is H or (C_{1-3}) alkyl;
especially wherein n is 2.

Additional interesting compounds are those of formula I wherein:
R_1 is X_1-(C_{3-7})-cycloalkane-(C_{1-6})alkylene- or X_2-(C_{3-9})cycloalkene-;
X_1 is hydrogen;
X_2 is hydrogen;

R_2, R_3, R_4 and R_5 independently are hydrogen or methyl;
R_6 is hydrogen;
R_7 is H or (C_{1-3})alkyl;
R_8 is H; and
n is 2.

In another embodiment, the invention provides pharmaceutical compositions, especially for the treatment of cancer in subjects, especially human, comprising a pharmaceutically acceptable carrier or diluent and an antitumorally effective dose of a compound of formula I above, or a pharmaceutically acceptable salt thereof, where possible.

In still another embodiment, the current invention provides a method for treating cancer comprising administering to a subject, especially human, in need of such treatment a therapeutically effective amount of a compound of formula I above, or a pharmaceutically acceptable salt thereof, where possible. The effective dosage of the compounds of the invention for such treatment may encompass a range of from about 0.01 milligrams per kilogram body weight per day to about 0.02 grams per kilogram of body weight per day.

In another embodiment, the current invention relates to the use of a compound of formula I or of a pharmaceutically acceptable salt of such a compound for the preparation of a pharmaceutical composition for use in the chemotherapy of cancer.

Furthermore, the current invention relates to the use of a compound of formula I or of a pharmaceutically acceptable salt of such a compound for the chemotherapy of cancer.

In the above definitions:
The alkyl groups, including any alkyl portion of a substituent, such as alkoxy, are either straight or branched chain, of which examples of the latter include isopropyl, isobutyl, *t*-butyl, isopentyl, neopentyl, isohexyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 1,1,2,2-tetramethylethyl unless otherwise noted.

The term "alkylene" as used herein refers to a straight or branched chain consisting solely of carbon and hydrogen. Examples of "alkylene" groups include methylene, ethylene, propylene, butylene, pentylene, and 3-methypentylene.

The term "alkenylene" as used herein refers to a straight or branched chain consisting solely of carbon and hydrogen, containing at least one carbon-carbon double bond. Examples of "alkenylene" groups include ethenylene, propenylene, butenylene, 3,3,-dimethylbut-1-enylene, 3-methylbut-1-enylene, pentenylene, 3-methylpentenylene, and butadiene.

The term "alkynylene" as used herein refers to a straight or branched chain divalent group consisting solely of carbon and hydrogen containing at least one carbon-carbon triple bond. Examples of "alkynylene" groups include acetylene, propynylene, butynylene, pentynylene, 3-methylpentynylene.

If R_2 and R_4 together or R_3 and R_5 together form an acetal group, R_2 and R_4 together or R_3 and R_5 together preferably form a group of the formula -C(R')(R")-, wherein R' and R" are selected independently of each other from X_1-(C_{1-6}) alkyl-, X_2-(C_{2-4}) alkenyl-, X_1-(C_{3-7})cycloalkyl-, or X_1-(C_{3-7})cycloalkane-(C_{1-3})alkyl- wherein X_1 is as defined herein.

The term "direct bond" as herein described refers to a single, double, or triple, covalent atomic bond which links together two moieties.

Halo is chloro, bromo, iodo or fluoro, especially chloro, bromo or iodo.

The substituent het is preferably a 3 to 9 membered aliphatic ring, such as a 4 to 7 membered aliphatic ring, containing from one to three heteroatoms selected from nitrogen, sulfur and oxygen, or het is a 5 to 7 member aromatic ring containing one or more heteroatoms, for example from 1 to 4 heteroatoms, selected from N, O and S, or het is a bicyclic and tricyclic fused ring system where each ring can independently be 5 or 6 membered and contain one or more heteroatoms, for example, 1, 2, 3, or 4 heteroatoms, chosen from O, N or S such that the fused ring system is aromatic. Examples of suitable het substituents include pyrrolidyl, tetrahydrofuryl, tetrahydrothiofuranyl, piperidyl, piperazyl, tetrahydropyranyl, morphilino, 1,3-diazapane, 1,4-diazapane, 1,4-oxazepane, 1,4-oxathiapane, furyl, thienyl, pyrrole, pyrazole, triazole, thiazole, oxazole, pyridine, pyrimidine, isoxazolyl, pyrazine, quinoline, isoquinoline, pyridopyrazine, pyrrolopyridine, furopyridine, indole, benzofuran, benzothiofuran, benzindole, benzoxazole, and pyrroloquinoline. Het is preferably pyridyl.

In the instance where het is a nitrogen containing ring, N-substituted compounds are included. Suitable N-substituents include (C_{1-14})alkyl, such as N-methyl or N-ethyl, -C(O)C_{1-12}alkyl, such as methylamido or ethylamido, -C(O)-O-(C_{1-14})alkyl, such as carbomethoxy or carboethoxy, or phenyl.

het also includes the above rings with substitution on one or more carbons. Suitable C-substituents include (C_{1-14})alkyl, such as methyl or ethyl, -OR_a, such as methoxy and ethoxy, -SR_a, halo, -$N(R_x)_2$ and the like.

Aryl includes phenyl and naphthyl substituents.

A "heteroaryl" group is mono-, bi- or tri-cyclic, and comprises 3-24, preferably 4-16 ring atoms, and is most preferably mono-cyclic comprising 5-7 ring atoms, wherein at least one or more, preferably one to four ring carbons are replaced by a heteroatom selected from O, N or S such as azirinyl, imidazolyl, thienyl, furyl, indolyl, pyranyl, thiopyranyl, thianthrenyl, isobenzofuranyl, benzofuranyl, 2*H*-pyrrolyl, pyrrolyl, benzimidazolyl, pyrazolyl, pyrazinyl, thiazolyl, isothiazolyl, dithiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3*H*-indolyl, benzimidazolyl, benzothiazolyl and benzo[1,2,5] thiadiazolyl, thiacumaryl, indazolyl, triazolyl, tetrazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, benzofuranyl, dibenzofuranyl, benzothiophenyl, dibenzothiophenyl, phthalazinyl, naphthyridinyl, quinoxalyl, quinazolinyl, cinnolinyl, pteridinyl, carbazolyl, carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, furazanyl, phenazinyl, phenothiazinyl, phenoxazinyl, chromenyl, isochromanyl and chromanyl, each of these radicals being unsubstituted or substituted by one to two substituents.

"Heterocyclic" refers to a heterocyclic radical containing 1-4 heteroatoms selected from nitrogen, oxygen and sulfur (e.g. piperazinyl, lower alkyl-piperazinyl, azetidinyl, pyrrolidinyl, piperidino, morpholinyl, imidazolinyl). The heterocyclic radical is preferably unsaturated, saturated or partially saturated in the bonding ring; has 3-24, more preferably 4-16 ring atoms, wherein at least in the bonding ring one or more, preferably 1-4, especially one or two carbon ring atoms are replaced by a heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, the bonding ring preferably having 4-12, especially 4-7 ring atoms; the heterocyclic radical is unsubstituted or substituted by one or more, especially 1-4

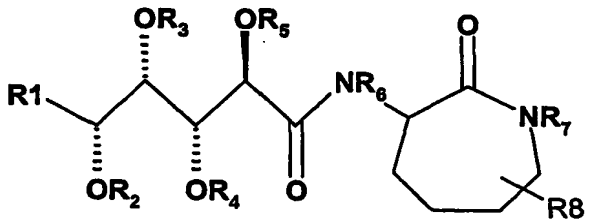
substituents and is especially selected from the group consisting of indoly, tetrahydrofuranyl, benzofuranyl, thienyl, pyridyl, imidazolinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidino, piperidyl, pyrrolidinyl, oxiranyl, 1,2-oxathiolanyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl and azetidinyl, with piperazinyl being especially preferred.

In view of the close relationship between the novel compounds in free form and in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the novel compounds, hereinbefore and hereinafter any reference to the free compounds is to be understood as referring also to the corresponding salts, as appropriate and expedient.

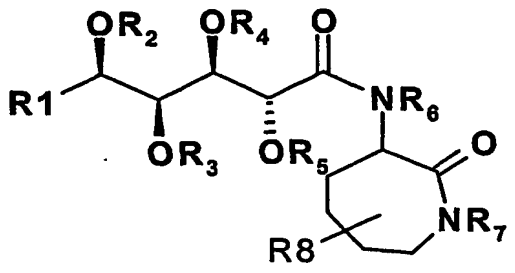
Salts are especially the pharmaceutically acceptable salts of compounds of formula I.

Salts of the compounds of formula I may be pharmaceutically acceptable acid or base addition salts with organic or inorganic acids or bases. Although the preferred acid addition salts are those of hydrochloric and methanesulfonic acid, for example, salts of sulfuric, phosphoric, citric, fumaric, maleic, benzoic, benzenesulfonic, succinic, tartaric, lactic and acetic acid may also be utilized.

Preferably, R_2, R_3, R_4 and R_5 are in the relative stereochemical conformation to each other depicted in stereochemical formulae Ia and Ib:

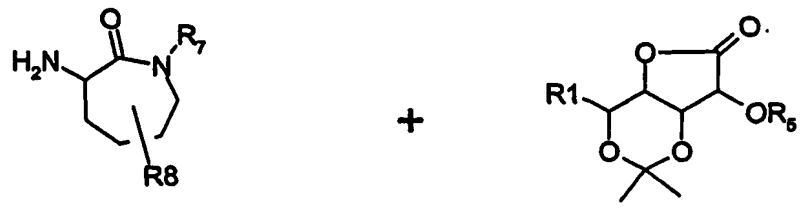


(Ia)



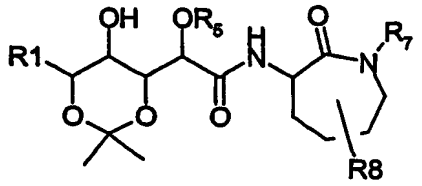
(Ib)

The lactams of formula I may be prepared as depicted below:



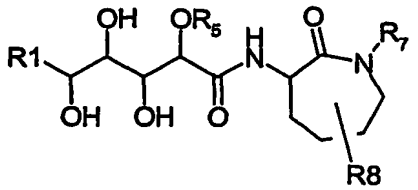
VI VII

Step A — acylation



VIII

Step B — hydrolysis



I

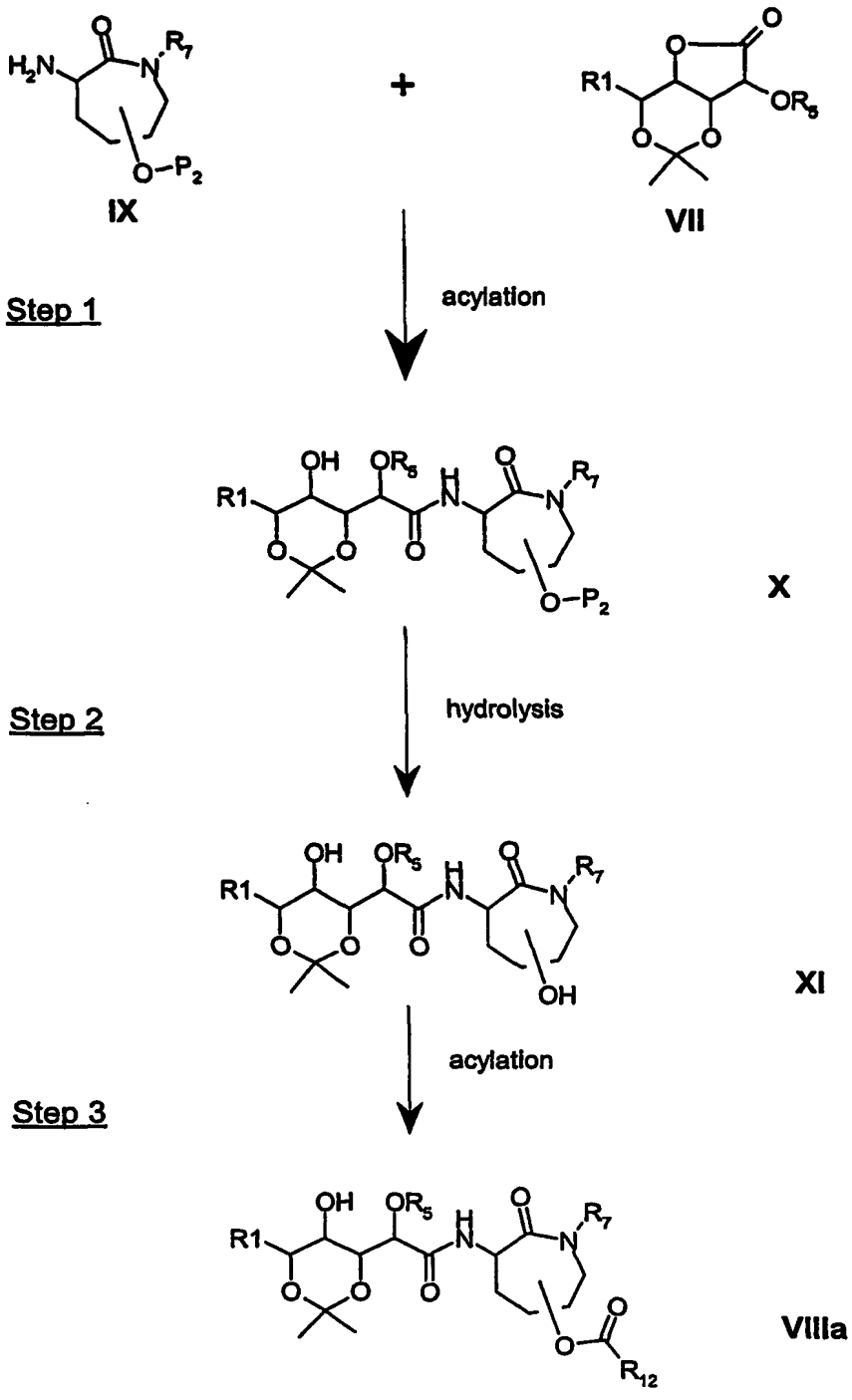
where each of R1, R_5, R_7 and R8 is as defined above.

As to the individual steps, Step A involves the acylation of an aminolactam of formula VI with a lactone compound of formula VII to obtain a diamide compound of formula VIII. The acylation is conducted in a polar, organic solvent, preferably a protic polar solvent such as isopropanol, at a temperature slightly below or at the reflux temperature of the solvent employed for a period of between 4 and 48 hours.

Alternatively, the acylation of an aminolactam of formula VI, or an acid addition salt thereof, with the lactone compound of formula VII in Step A may be carried out with in the presence of: 1) a weak base, preferably a carboxylate salt such as sodium 2-ethylhexanoate, and 2) a polar, organic solvent, preferably an ether such as tetrahydrofuran, at a temperature of between 0°C and 50°C, preferably at 25°C, for a period of between 1 hour and 7 days, preferably for 20 hours.

Step B concerns the hydrolysis of the 1,3-dioxane group common to a diamide compound of formula VIII, to obtain a substituted lactam compound of formula I. The hydrolysis is typically carried out by dissolving the diamide in a mixture of solvents consisting of 1) a protic acid, preferably an organic acid such as trifluoroacetic acid, 2) a protic solvent, preferably water, and 3) an inert organic solvent, preferably a cyclic ether such as tetrahydrofuran, at a temperature of between 0 °C and 25 °C for a period of between 5 minutes and 2 hours.

Alternatively, the diamide compounds of formula VIIIa may be prepared according to the following 3-step reaction scheme:



where R_1, R_5, and R_7 are as defined above, R_{12} is an appropriate substituent based on the definition of R8 above, and P_2 is an alcohol protective group. Preferably, P_2 is a silyl group such as *tert*-butyldimethylsilyl.

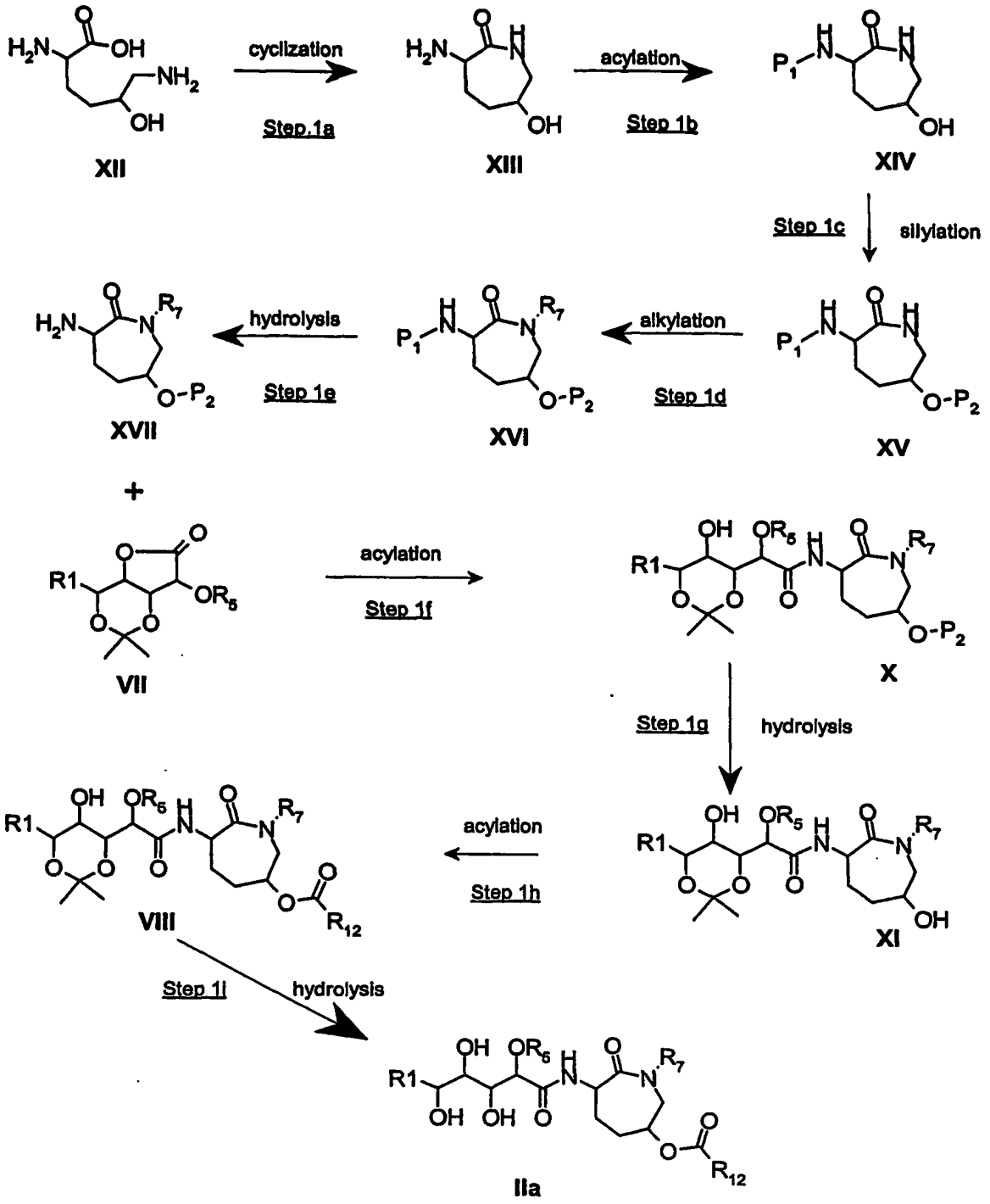
As to the individual steps, Step 1 involves the acylation of an aminolactam of formula IX with a lactone compound of formula VII to obtain a diamide compound of formula X. The acylation is conducted in the presence of a base, preferably an alkylamine base such as diisopropylethylamine, and a polar, organic solvent, preferably a protic polar solvent such as isopropanol, at a temperature slightly below or at the reflux temperature of the solvent employed for a period of between 4 and 48 hours.

Step 2 concerns the hydrolysis of the group P_2 common to a diamide compound of formula X to obtain a hydroxylactam compound of formula XI. The hydrolysis is typically carried out in the presence of fluoride, preferably a fluoride salt such as tetrabutyl-ammonium fluoride, and an inert organic solvent, preferably a cyclic ether such as tetrahydrofuran, at a temperature of between 0 °C and 25 °C for a period of between 5 minutes and 2 hours.

Step 3 concerns the acylation of a hydroxylactam compound of formula XI by reacting it with an acid chloride of formula $R_{12}COCl$ where R_{12}, is defined above, to obtain a diamide compound of formula VIIIa. The acylation is conducted in the presence of a base, preferably an alkylamine base such as triethylamine, and an inert organic solvent, preferably a chlorinated alkane such as dichloromethane, at a temperature of between -78 °C and 25 °C for a period of between 1 and 24 hours.

Alternatively, the acylation of a hydroxylactam compound of formula XI in Step 3 may be carried out with a carboxylic acid of formula $R_{12}COCl$ where R_{12}, is defined above, in the presence of a carboxylic acid coupling reagent, preferably a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, and a suitable activating agent common to diimide coupling reactions, preferably a substituted pyridine such a 4-dimethylaminopyridine, and an inert organic solvent, preferably a chlorinated alkane such as dichloromethane, at a temperature of between -78 °C and 25 °C for a period of between 1 and 24 hours.

The aminolactam compounds of formula Ia may be prepared as depicted below:



where each R1, R_5, R_7 and R_{12} is as defined above, and P_1 is a carbonyl-containing group. Preferably, P_1 is alkoxycarbonyl such as *t*-butyloxycarbonyl. P_2 is an alcohol protective group. Preferably, P_2 is a silyl group such as *tert*-butyldimethylsilyl.

As to the individual steps, Step 1a involves the cyclization of hydroxylysine (or any salt or hydrate preparation thereof) XII to obtain hydroxycyclolysine XIII. The cyclization is typically carried out in the presence of a coupling reagent, preferably a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, and a suitable activating agent common to diimide coupling reactions, preferably an *N*-hydroxy compound such as 1-hydroxybenztriazole hydrate, and a base, preferably an alkylamine base such as triethylamine, and a polar organic solvent, preferably an amide such as *N,N*-dimethylformamide, at a temperature of between 0 °C and 40 °C for a period of between 12 and 72 hours.

Step 1b involves the *N*-acylation of hydroxycyclolysine XIII to obtain an *N*-acylhydroxycyclolysine compound of formula XIV. The acylating agent is typically an acid chloride or an anhydride. When P_1 is *t*-butyloxycarbonyl, the acylating agent is di-*tert*-butyldicarbonate. The reaction is carried out in the presence of a base, preferably an alkylamine base such as triethylamine, and a polar organic solvent, preferably an amide such as *N,N*-dimethylformamide, at a temperature of between 0 °C and 40 °C for a period of between 1 and 24 hours.

Step 1c involves the *O*-silylation of an *N*-acylhydroxycyclolysine compound of formula XIV to obtain a silyl ether compound of formula XV. The silylating agent is typically a silyl chloride or trifluoromethanesulfonate. When P_2 is *tert*-butyldimethylsilyl, the silylating agent is *tert*-butyldimethylsilylchloride. The reaction is carried out in the presence of a base, preferably a mild base such as imidazole, and a polar organic solvent, preferably an amide such as *N,N*-dimethylformamide, at a temperature of between 0 °C and 40 °C for a period of between 1 and 24 hours.

Step 1d involves the *N*-alkylation of a silyl ether compound of formula XV with an alkyl (defined as R_7 above) halide or sulfonate to obtain an *N*-alkyl lactam compound of formula XVI. The alkylation is conducted in the presence of a strong base, preferably an alkali metal amide such as sodium bis(trimethylsilyl)amide, and an inert organic solvent, preferably a cyclic ether such as tetrahydrofuran, at a temperature of between -100 °C and 25 °C for a period of between 5 minutes and 2 hours.

Step 1e concerns the hydrolysis of the group P_1 on an N-alkyl lactam compound of formula XVI. The hydrolysis is typically carried out in the presence of a protic acid, preferably an organic acid such as trifluoroacetic acid, hydrogen or a silyl halide, preferably a silyl iodide such as trimethylsilyl iodide, and an inert organic solvent, preferably a chlorinated alkane such as dichloromethane, at a temperature of between -100 °C and 25 °C for a period of between 1 minute and 2 hours.

Step 1f involves the acylation of an aminolactam of formula XVII with a lactone compound of formula VII to obtain a diamide compound of formula X. The acylation is conducted in the presence of a base, preferably an alkylamine base such as diisopropylethylamine, and a polar, organic solvent, preferably a protic polar solvent such as isopropanol, at a temperature slightly below or at the reflux temperature of the solvent employed for a period of between 4 and 48 hours.

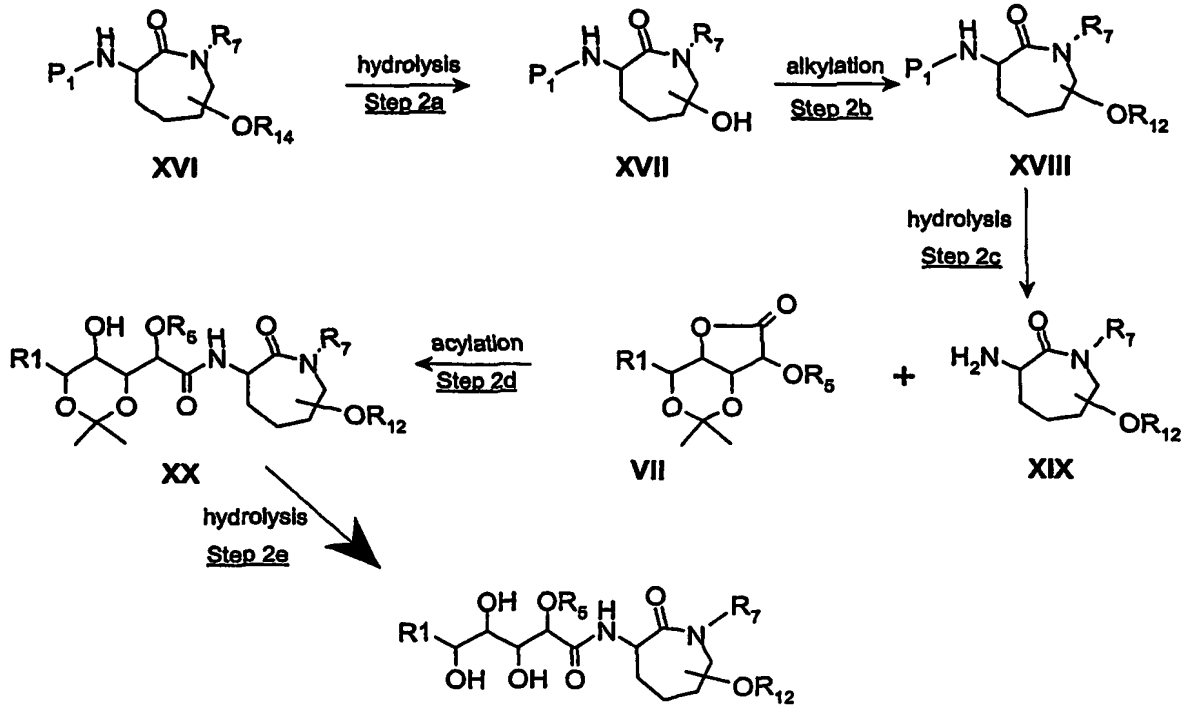
Step 1g concerns the hydrolysis of the group P_2 common to an N-alkyl lactam compound of formula X, to obtain a hydroxylactam compound of formula XI. The hydrolysis is typically carried out in the presence of fluoride, preferably a fluoride salt such as tetrabutylammonium fluoride, and an inert organic solvent, preferably a cyclic ether such as tetrahydrofuran, at a temperature of between 0 °C and 25 °C for a period of between 5 minutes and 6 hours.

Step 1h concerns the acylation of a hydroxylactam compound of formula XI by reacting it with an acid chloride of formula $R_{12}COCl$ where R_{12}, is defined above, to obtain a diamide compound of formula VIII. The acylation is conducted in the presence of a base, preferably an alkylamine base such as triethylamine, and an inert organic solvent, preferably a chlorinated alkane such as dichloromethane, at a temperature of between -78 °C and 25 °C for a period of between 1 and 24 hours.

Step 1i concerns the hydrolysis of the 1,3-dioxane group of compound formula VIII, to obtain a substituted lactam compound of formula I. The hydrolysis is typically carried out by dissolving the diamide in a mixture of solvents consisting of 1) a protic acid, preferably an organic acid such as trifluoroacetic acid, 2) a protic solvent, preferably water, and 3) an inert organic solvent, preferably a cyclic ether such as tetrahydrofuran, at a temperature of between 0 °C and 25 °C for a period of between 5 minutes and 2 hours.

Alternatively, the acylation of a hydroxylactam compound of formula XI in Step 1h may be carried out with a carboxylic acid of formula $R_{12}COOH$ where R_{12}, is defined, in the presence of a carboxylic acid coupling reagent, preferably a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, and a suitable activating agent common to diimide coupling reactions, preferably a substituted pyridine such a 4-dimethylaminopyridine, and an inert organic solvent, preferably a chlorinated alkane such as dichloromethane, at a temperature of between -78 °C and 25 °C for a period of between 1 and 24 hours.

The aminolactam compounds of formula IIb may be prepared as depicted below:



R_{14} is a leaving group.

where each R1, R_5, R_7 and R_{12} is as defined above, and P_1 is a carbonyl-containing group. Preferably, P_1 is alkoxycarbonyl such as *t*-butyloxycarbonyl. P_2 is an alcohol protective group. Preferably, P_2 is a silyl group such as *tert*-butyldimethylsilyl.

Step 2a concerns the hydrolysis of the group P_2 common to an N-alkyl lactam compound of formula XVI, to obtain a hydroxylactam compound of formula XVII. The hydrolysis is typically carried out in the presence of fluoride, preferably a fluoride salt such as tetrabutylammonium fluoride, and an inert organic solvent, preferably a cyclic ether such as tetrahydrofuran, at a temperature of between 0 °C and 25 °C for a period of between 5 minutes and 6 hours.

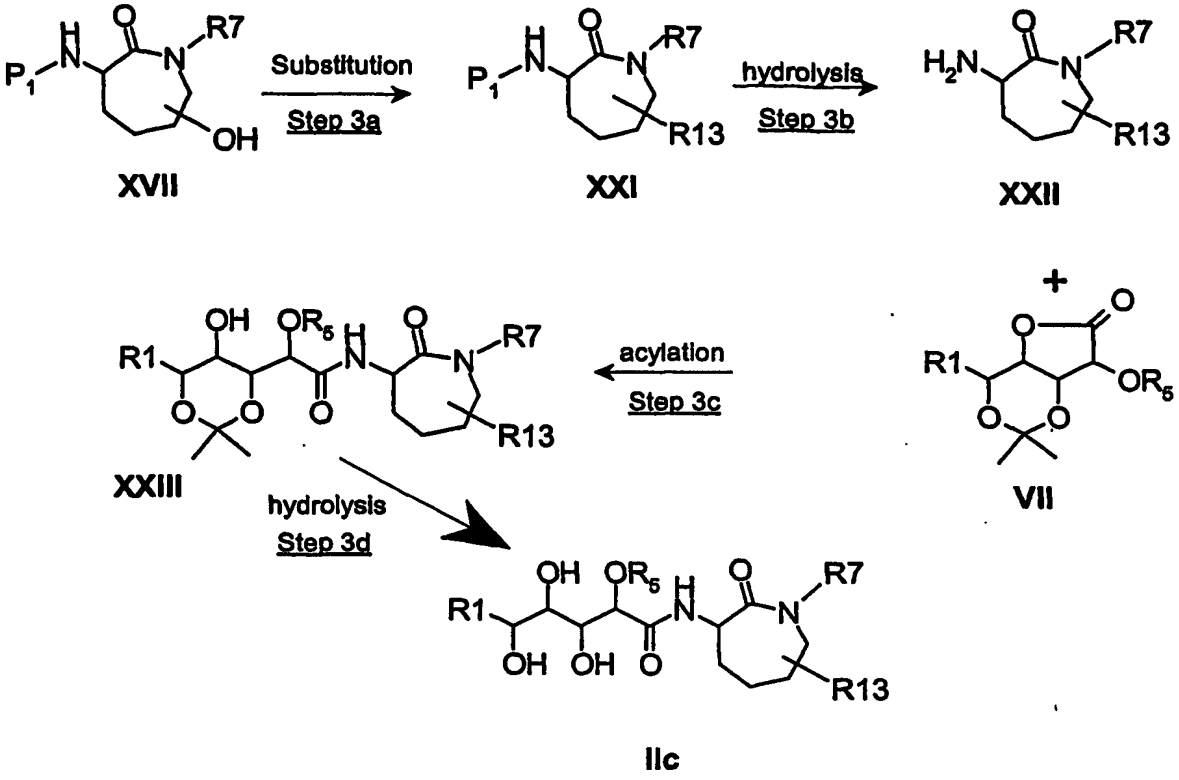
Step 2b involves the O-alkylation of a compound of formula XVII with an alkyl (defined as R_{12} above) halide or sulfonate to obtain an O-alkyl lactam compound of formula XVI. The alkylation is conducted in the presence of a strong base, preferably an alkali metal amide such as sodium bis(trimethylsilyl)amide, and an inert organic solvent, preferably a cyclic ether such as tetrahydrofuran, at a temperature of between -100 °C and 25 °C for a period of between 5 minutes and 6 hours.

Step 2c concerns the hydrolysis of the group P_1 on an N-alkyl lactam compound of formula XVIII. The hydrolysis is typically carried out in the presence of a protic acid, preferably an organic acid such as trifluoroacetic acid, hydrogen or a silyl halide, preferably a silyl iodide such as trimethylsilyl iodide, and an inert organic solvent, preferably a chlorinated alkane such as dichloromethane, at a temperature of between -100 °C and 25 °C for a period of between 1 minute and 2 hours.

Step 2d involves the acylation of an aminolactam of formula XIX with a lactone compound of formula VII to obtain a diamide compound of formula XX. The acylation is conducted in the presence of a base, preferably an alkylamine base such as diisopropylethylamine, and a polar, organic solvent, preferably a protic polar solvent such as isopropanol, at a temperature slightly below or at the reflux temperature of the solvent employed for a period of between 4 and 48 hours.

Step 2e concerns the hydrolysis of the 1,3-dioxane group of compound formula XX, to obtain a substituted lactam compound of formula I. The hydrolysis is typically carried out by dissolving the diamide in a mixture of solvents consisting of 1) a protic acid, preferably an organic acid such as trifluoroacetic acid, 2) a protic solvent, preferably water, and 3) an inert organic solvent, preferably a cyclic ether such as tetrahydrofuran, at a temperature of between 0 °C and 25 °C for a period of between 5 minutes and 2 hours.

The aminolactam compounds of formula IIc may be prepared as depicted below:



XVII XXI XXII

XXIII VII

IIc

where each R1, R_5, R7 is as defined above, R13 is an appropriate substituent based on the definition of R_8 above and P_1 is a carbonyl-containing group.

Preferably, P_1 is alkoxycarbonyl such as *t*-butyloxycarbonyl.

Step 3a involves the substitution of the hydroxy group of the compound of formula XVII for a heteroatom (defined as Y above) preferably with inversion of configuration and most preferably by a Mitsunobu type reaction (reference) involving a trialkyl or triaryl substituted phosphine, an azodicarboxylate diester and a nucleophile source such as diphenylphosphoryl azide. Alternatively the hydroxy group can be converted to a sulfonate or halide suitable for displacement.

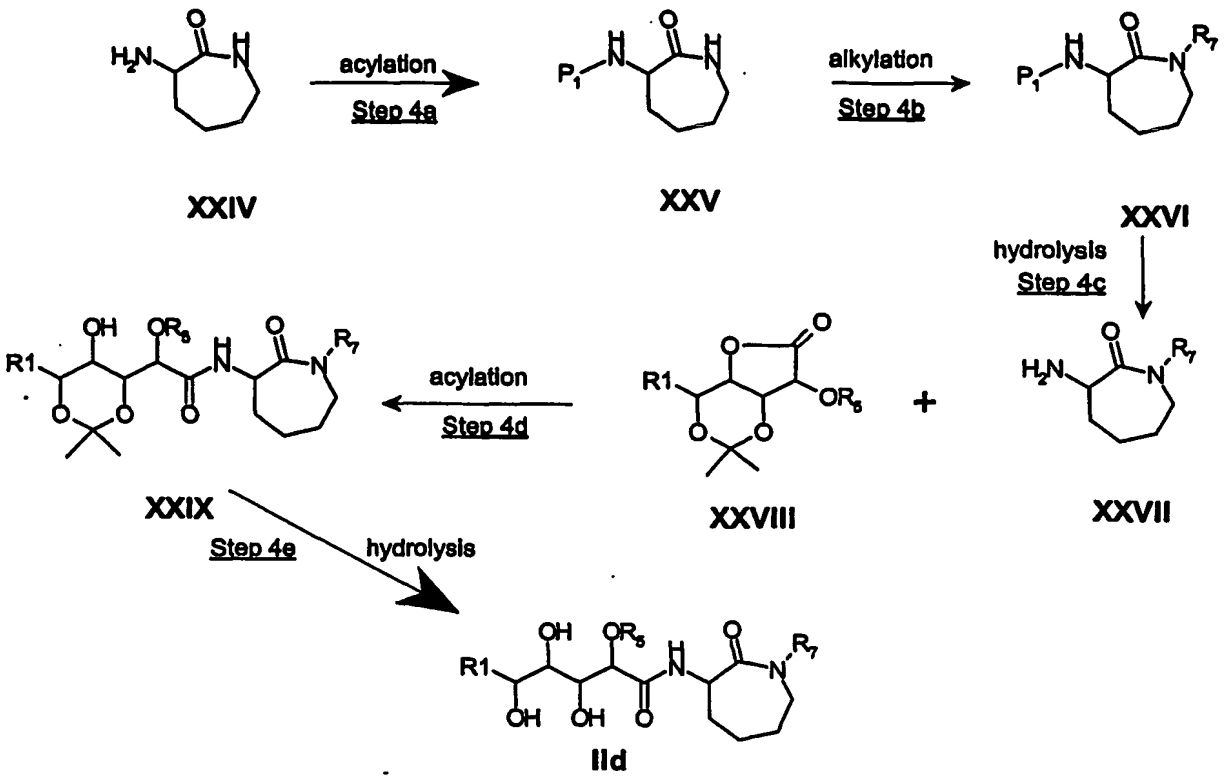
Step 3b concerns the hydrolysis of the group P_1 on an N-alkyl lactam compound of formula XXI. The hydrolysis is typically carried out in the presence of a protic acid, preferably an

organic acid such as trifluoroacetic acid, hydrogen or a silyl halide, preferably a silyl iodide such as trimethylsilyl iodide, and an inert organic solvent, preferably a chlorinated alkane such as dichloromethane, at a temperature of between -100 °C and 25 °C for a period of between 1 minute and 2 hours.

Step 3c involves the acylation of an aminolactam of formula XXII with a lactone compound of formula VII to obtain a diamide compound of formula XXIII. The acylation is conducted in the presence of a base, preferably an alkylamine base such as diisopropylethylamine, and a polar, organic solvent, preferably a protic polar solvent such as isopropanol, at a temperature slightly below or at the reflux temperature of the solvent employed for a period of between 4 and 48 hours.

Step 3d concerns the hydrolysis of the 1,3-dioxane group of compound formula XXIII, to obtain a substituted lactam compound of formula I. The hydrolysis is typically carried out by dissolving the diamide in a mixture of solvents consisting of 1) a protic acid, preferably an organic acid such as trifluoroacetic acid, 2) a protic solvent, preferably water, and 3) an inert organic solvent, preferably a cyclic ether such as tetrahydrofuran, at a temperature of between 0 °C and 25 °C for a period of between 5 minutes and 2 hours.

The aminolactam compounds of formula IId may be prepared as depicted below:



where each R1, R_5, and R_7 is as defined above, and P_1 is a carbonyl-containing group. Preferably, P_1 is alkoxycarbonyl such as *t*-butyloxycarbonyl.

Step 4a involves the *N*-acylation of cyclolysine XXIV to obtain an *N*-acylcyclolysine compound of formula XXV. The acylating agent is typically an acid chloride or an anhydride. When P_1 is *t*-butyloxycarbonyl, the acylating agent is di-*tert*-butyldicarbonate. The reaction is carried out in the presence of a base, preferably an alkylamine base such as triethylamine, and a polar organic solvent, preferably an amide such as *N,N*-dimethylformamide, at a temperature of between 0 °C and 40 °C for a period of between 1 and 24 hours.

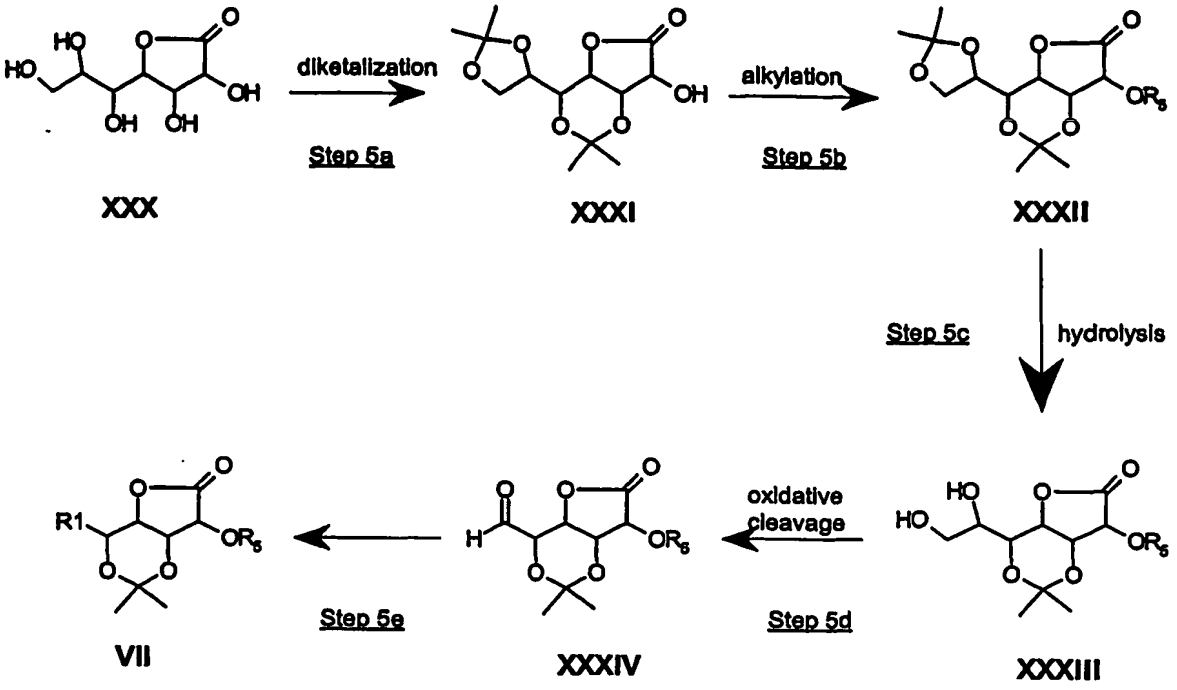
Step 4b involves the *N*-alkylation of an *N*-acylcyclolysine compound of formula XXV with an alkyl (defined as R_7 above) halide or sulfonate to obtain an *N*-alkyl lactam compound of formula XXVI. The alkylation is conducted in the presence of a strong base, preferably an alkali metal amide such as sodium bis(trimethylsilyl)amide, and an inert organic solvent, preferably a cyclic ether such as tetrahydrofuran, at a temperature of between -100 °C and 25 °C for a period of between 5 minutes and 2 hours.

Step 4c concerns the hydrolysis of the group P_1 on an N-alkyl lactam compound of formula XXVI, The hydrolysis is typically carried out in the presence of a protic acid, preferably an organic acid such as trifluoroacetic acid, hydrogen or a silyl halide, preferably a silyl iodide such as trimethylsilyl iodide, and an inert organic solvent, preferably a chlorinated alkane such as dichloromethane, at a temperature of between -100 °C and 25 °C for a period of between 1 minute and 2 hours.

Step 4d involves the acylation of an aminolactam of formula XVII with a lactone compound of formula XXVII to obtain a diamide compound of formula XXIX. The acylation is conducted in the presence of a base, preferably an alkylamine base such as diisopropylethylamine, and a polar, organic solvent, preferably a protic polar solvent such as isopropanol, at a temperature slightly below or at the reflux temperature of the solvent employed for a period of between 4 and 48 hours.

Step 4e concerns the hydrolysis of the 1,3-dioxane group of compound formula XXIX, to obtain a substituted lactam compound of formula Id. The hydrolysis is typically carried out by dissolving the diamide in a mixture of solvents consisting of 1) a protic acid, preferably an organic acid such as trifluoroacetic acid, 2) a protic solvent, preferably water, and 3) an inert organic solvent, preferably a cyclic ether such as tetrahydrofuran, at a temperature of between 0 °C and 25 °C for a period of between 5 minutes and 2 hours.

The lactone compounds of formula VII may be prepared as depicted below:



where R1 and R_5 are as defined above.

As to the individual steps, Step 5a involves the diketalization of polyhydroxylated lactone of formula XXX with acetone to obtain bis(acetonide) XXXI. The diketalization is conducted in acetone as solvent using a catalyst such as iodine at a temperature of between 0 °C and the reflux temperature for a period of between 2 and 48 hours.

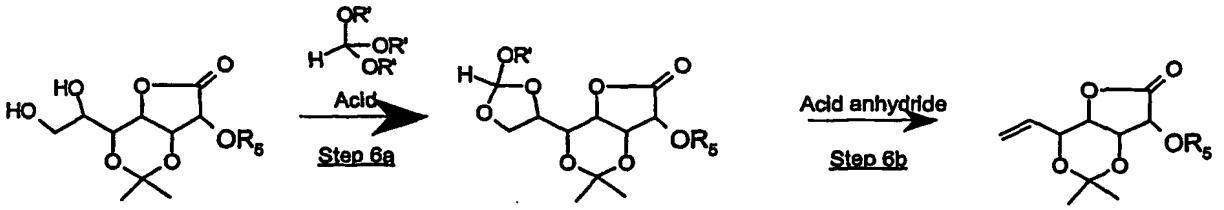
Step 5b involves the alkylation of *bis*(acetonide) XXXI with an alkylating agent such as an alkyl (defined as R_5 above) halide, sulfonate or sulfate ester to obtain the ether XXXII. The alkylation is conducted in the presence of water and a base, preferably a metal oxide such as silver oxide, and an inert organic solvent, preferably a chlorinated alkane such as dichloromethane, at a temperature of between 0 °C and the reflux temperature for a period of between 12 hours and 7 days.

Step 5c involves the hydrolysis of alkyl ether XXXII to obtain the dihydroxy compound of formula XXXIII. The hydrolysis is conducted in the presence of water and a protic acid, preferably a carboxylic acid such as acetic acid, at a temperature of between 5 °C and 35 C for a period of between 1 and 24 hours.

Step 5d involves the oxidative cleavage of dihydroxy compound XXXIII to obtain the aldehyde XXXIV. The reaction is conducted in the presence of an oxidant, preferably a periodate salt such as sodium periodate, in a protic solvent, preferably an alkanol such as methanol, at a temperature of between 0 °C and 25 °C for a period of between 10 minutes and 4 hours.

Step 5e involves the olefination of aldehyde XXXIV to obtain a lactone compound of formula VII. The olefination is conducted in the presence of an organometallic compound, preferably an organochromium compound such as the transient species generated from chromium(II)chloride and a diiodoalkane (defined as R_1CHI_2 where R_1 is as defined above), in the presence of a solvent mixture consisting of 1) a polar organic solvent, preferably an amide such as *N,N*-dimethylformamide, and 2) an inert organic solvent, preferably a cyclic ether such as tetrahydrofuran, at a temperature of between -80 °C and 25 °C for a period of between 5 minutes and 4 hours.

Alternatively the lactone compounds of formula VIIa may be prepared as depicted below:

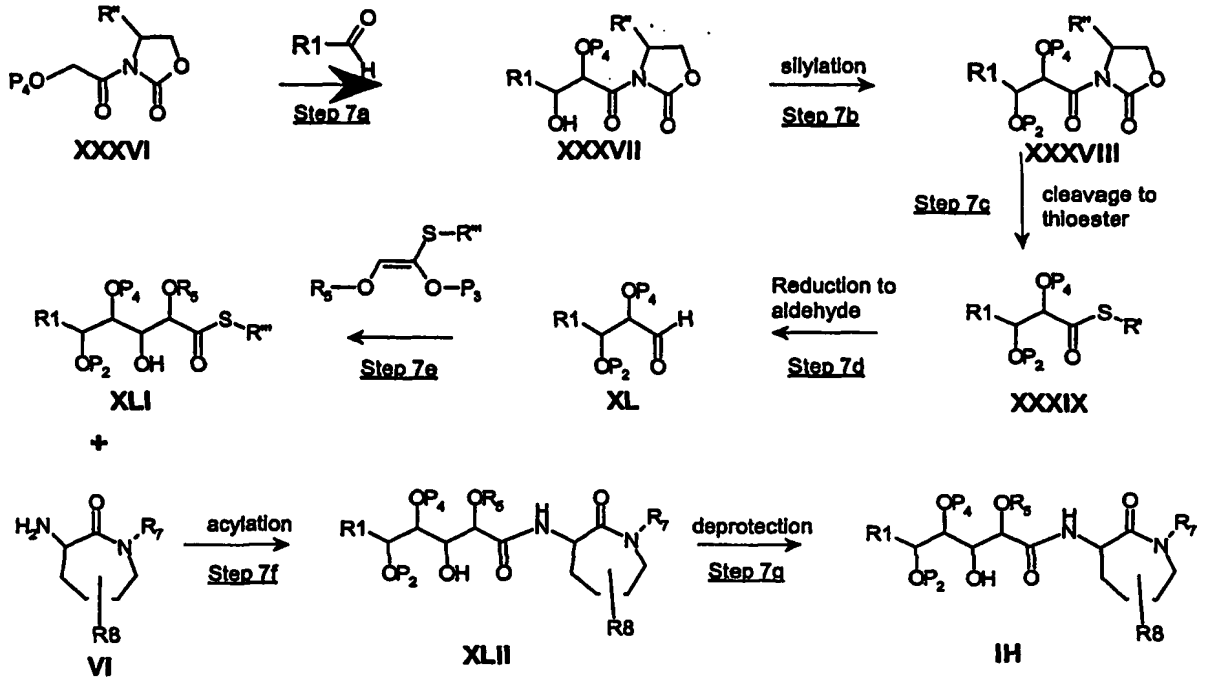


where R_5 is defined above and R' is $C_{(1-6)}$ alkyl

Step 6a involves the conversion of XXXIII to an ortho ester XXXV by acid catalyzed transesterification with an alkyl orthoester, preferably triethylorthoformate and p-toluenesulfonic acid. The reaction can be run with excess alkyl orthoester as the solvent or an inert organic solvent may be used at a temperature of between 20 °C and 80 °C for a period between 1 and 24 hours.

Step 6b involves the elimination of the orthoester XXXV to give alkene VIIa. The reaction is conducted in an organic acid anhydride, preferably acetic anhydride at a temperature of 20 °C and 100 °C for a period between 1 and 24 hours.

Alternatively the lactams of formula I may be prepared as depicted below:



where each R1, R_5, R_7, R_9, and X are defined above, R" is a $C_{(3-9)}$ branched alkyl or phenyl substituted $C_{(1-3)}$ alkyl, preferably benzyl and R'" is a $C_{(1-6)}$ alkyl, preferably ethyl. P_2 and P_3 are alcohol protective groups, preferably silyl groups such as *tert*-butyldimethylsilyl and trimethylsilyl respectively. P_4 is an alcohol protective group, preferably benzyl or 2-naphthlmethyl ethers.

Step 7a involves an Evans type aldol condensation of oxyimide XXXVI with an aldehyde to give XXXVII. The reaction is conducted in the presence of a Lewis acid, preferably diethylborontriflate and an organic base, preferably diisopropylethylamine in an inert organic solvent such as CH_2Cl_2 at a temperature of between –100 °C and 0 °C for a period of 1-24 hours.

Step 7b involves the O-silylation of compound XXXVII to obtain a silyl ether compound of formula XXXVIII. The silylating agent is typically a silyl chloride or trifluoromethanesulfonate.

When P_2 is *tert*-butyldimethylsilyl, the silylating agent is *tert*-butyldimethylsilylchloride. The reaction is carried out in the presence of a base, preferably a mild base such as imidazole, and a polar organic solvent, preferably an amide such as *N,N*-dimethylformamide, at a temperature of between 0 °C and 40 °C for a period of between 1 and 24 hours.

Step 7c involves the formation of thioester XXXIX from XXXVIII by reaction with an alkali metal salt of a thioether, preferably LiSEt, in an inert solvent, preferably THF, at a temperature of between –100 °C and 0 °C for a period of 1-24 hours.

Step7d involves conversion of thioester XXXIX to the aldehyde XL by reduction with a metal hydride, preferably diisobutylaluminum hydride, in an inert solvent, preferably CH_2Cl_2, at a temperature of between –100 °C and 0 °C for a period of 10 minutes to 1 hour.

Step 7e involves a Gennari type coupling of aldehyde XL with a thiovinylether to give the thioester XLI. The reaction is conducted in the presence of a Lewis acid, preferably $SnCl_4$, in an inert solvent, preferably a mixture of CH_2Cl_2 and heptane, at a temperature of between –100 °C and 0 °C for a period of 1-24 hours.

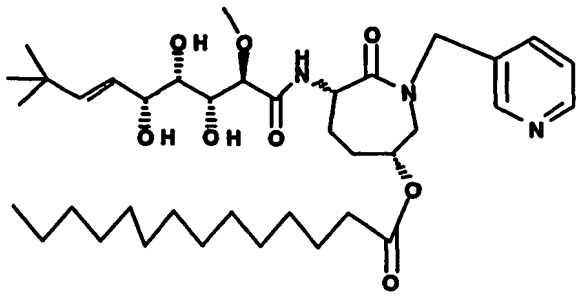
Step 7f involves the acylation of thioester XLI with amine VI to give diamide XLII. The reaction is conducted in an inert solvent, preferably dioxane, at a temperature of between room temperature and 100 °C for a period of 1-48 hours.

Step 7g involves the deprotection of diamide XLII to give compound I. The method employed is dependant on the P_2 and P_5 groups utilized, preferably when P_2 is *tert*-butyldimethylsilyl and P_4 is 2-naphthlmethyl ether a two step procedure is employed using DDQ in a mixture of wet CH_3OH and CH_2Cl_2 followed by treatment with tetrabutylammonium fluoride in THF to give compound I.

The following specific examples are intended to further illustrate, but not limit, the invention.

EXAMPLES

EXAMPLE 1: Tetradecanoic acid (3R,6S)-7-oxo-1-pyridin-3-ylmethyl-6-((2R,3R,4S,5R)-(E)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-non-6-enoylamino)-azepan-3-yl ester



a) Preparation of 3,5:6,7-bis-O-(1-methylethylidene)-α-D-glucoheptonic γ-lactone. α-D-Glucoheptonic γ-lactone (500 g, 2.4 mol) is added into 9 L of acetone in a 5 gal plastic drum. The mixture is agitated mechanically until most of the solid dissolved (15-20 min). Iodine (60g, 0.236 mol) is added portion wise into the lactone solution over 5-10 min. The resulting mixture is stirred overnight. A saturated solution of $Na_2S_2O_3$ (1.3 L) is added to the iodine solution to quench the reaction. The resulting solution is concentrated to about half of its original volume in vacuum, and brine solution (5 L) is added. The resulting mixture is extracted with 3 x 1.2 L EtOAc. All organic layers are combined and evaporated to dryness. The solid is slurried with a mixture of ether and hexane (3:7), and filtered. The filter cake is washed with Et_2O (50 mL) and air dried, giving 599 g of the desired compound as a white powder (86.5%): ^1H NMR ($CDCl_3$) δ 4.62 (m, 1H), 4.50 (m, 1H), 4.35 (m, 2H), 4.07 (m, 1H), 3.93 (m, 1H), 3.82 (dd, 1H), 3.08 (d, 1H), 1.51 (s, 3H), 1.44 (s, 3H), 1.39 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 174.4, 109.4, 98.6, 72.8, 71.4, 69.3, 68.4, 67.8, 66.7, 28.6, 26.7, 24.6, 19.3.

Preparation of 2-O-methyl-3,5:6,7-bis-O-(1-methylethylidene)-α-D-glucoheptonic γ-lactone. 3,5:6,7-bis-O-(1-methylethylidene)-α-D-glucoheptonic γ-lactone (719 g, 2.49 mol) is added into 4.5 L of CH_2Cl_2 in a 5 gal plastic drum. The mixture is stirred under N_2. Iodomethane (2500 g, 17.6 mol) is added immediately followed by addition of silver(I) oxide (1750 g, 7.58 mol). Water (30 mL) is added to the reaction mixture. Ice bath is used to maintain the reaction temperature at 15-30 °C. The reaction is stirred in the absence of light for 18 h. After diluting the reaction mixture with 1.5 L of CH_2Cl_2, the solid is filtered and washed with an additional 2.2 L of CH_2Cl_2. The undesired solid is discarded and the filtrate is evaporated

to dryness. The residue is slurried in Et_2O (1.5 L), filtered, and dried to give 618 g product (82 %): ^1H NMR ($CDCl_3$) δ 4.75 (m, 1H), 4.33 (m, 1H), 4.29 (m, 1H), 4.15 (m, 1H), 4.07 (m, 1H), 3.96 (dd, 1H), 3.83 (dd, 1H), 3.65 (s, 3H), 1.57 (s, 3H), 1.42 (s, 6H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.5, 109.6, 98.5, 79.0, 73.1, 69.5, 68.6, 67.5, 66.9, 59.1, 28.9, 26.9, 24.9, 19.4.

Preparation of 2-*O*-Methyl-3,5-*O*-(1-methylethylidene)-α-D-glucoheptonic γ-lactone. 2-*O*-methyl-3,5:6,7-bis-*O*-(1-methylethylidene)-α-D-glucoheptonic γ-lactone (618 g, 2.05 mol) is dissolved in 8 L of a mixture of acetic acid and water (1:1) over 30 min. The solution is stirred at ambient temperature overnight. The solution is evaporated to dryness *in vacuum*. The solid is slurried in 3-5 L of hot acetone and filtered. After oven drying at 20-30 °C, 363 g of the desired compound is obtained (67.6 %). ^1H NMR($CDCL_3$): δ 4.92 (d, 1H), 4.80 (m, 1H), 4.47 (d, 1H), 4.42 (t, 1H), 4.39 (m, 1H), 3.95 (dd, 1H), 3.75 (m, 2H), 3.4 (s, 3H), 2.5 (m, 1H), 1.42 (s, 3H), 1.22 (s, 3H).

d) Preparation of 2,4-*O*-(1-methylethylidene)-5-*O*-methyl-L-glucuronic γ-lactone. 2-*O*-Methyl-3,5-*O*-(1-methylethylidene)-α-D-glucoheptonic γ-lactone (200 g, 0.76 mol) is dissolved into a 1:1 mixture of methanol and water (3.6 L). The stirred mixture is cooled in an ice water bath to about 8 °C. Solid $NaIO_4$ (213 g, 0.98 mol) is added portion wise. Reaction is complete within 40 min as indicated by thin layer chromatography (TLC) (silica gel, 5% methanol, 15% EtOAc in CH_2Cl_2). Solid NaCl is added into the reaction mixture to saturate the methanolic solution. The solid is filtered and washed with 2 L CH_2Cl_2. The filtrate is extracted with 7x500 mL CH_2Cl_2. Combined organic layers are dried over Na_2SO_4, filtered and concentrated to a syrup, which formed a precipitate upon addition of hexane. The solid is filtered and rinsed with Et_2O. A portion of the crude product (50 g) is dissolved in 3 L $CHCl_3$ and heated to reflux. After rotary evaporation of 2.1 L of $CHCl_3$ at atmospheric pressure (methanol is driven out of the system by co-evaporation with $CHCl_3$) the residue is evaporated to dryness. 44 g of the desired product is obtained as a solid after drying *in vacuum* overnight. ^1H NMR (CDCl3): δ 9.60 (s, 1H), 4.78 (m, 1H), 4.42 (s, 2H), 4.15 (dd, 1H), 3.65 (s, 3H), 1.58 (s, 3H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 198.8, 171.9, 99.0, 78.4, 74.4, 72.9, 68.4, 67.4, 59.2, 28.7, 19.0.

e) Preparation of (6*E*)-6,7,8,9-tetradeoxy-8,8-dimethyl-2-O-methyl-3,5-*O*-(1-methylethylidene)-gulo-non-6-enonic acid lactone.

into a 2 L round bottom flask, is added $CrCl_2$ (50 g, 41 mmol), anhydrous THF (750 mL), and DMF (32 mL). The mixture is stirred under N_2 for 1 h. A solution of 2,4-*O*-(1-methylethylidene)-5-O-methyl-L-glucuronic γ-lactone (12 g, 50 mmol), 1,1-diiodo-2,2-dimethylpropane (15 mL), and 500 mL of anhydrous THF is added slowly into the reaction mixture. After the addition, the reaction mixture is stirred at ambient temperature for 1.5 h. The reaction is quenched with saturated aqueous NH_4Cl. The residue is partitioned with EtOAc/water and chromatographed (5% EtOAc - CH_2Cl_2) to give 9 g (63%) of the desired compound as a white crystalline solid: ^{1}HNMR ($CDCl_3$) δ 5.82 (d, 1H), 5.58 (q, 1H), 4.71 (m, 1H), 4.46 (m, 1H), 4.10 (dd, 1H), 4.0 (m, 1H), 3.66 (s, 3H), 1.58 (s, 3H), 1.53 (s, 3H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.5, 147.0, 120.2, 98.7, 79.1, 71.9, 70.3, 67.6, 59.2, 33.2, 29.3, 19.3.

Preparation of (3*S*, 6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-hydroxy-2*H*-azepin-2-one In a 1 L flask (5*R*)-5-hydroxy-L-lysine (10 g, 0.040 mol), 1-hydroxybenzotriazole hydrate (8.2 g, 0.060 mol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide-HCl (11.6 g, 0.060 mol) are added to 500 mL DMF with stirring. After 0.5 h triethylamine (16.8 mL, 0.120 mol) is added. The reaction is stirred at room temperature for 48 h. Di-*tert*-butyl dicarbonate (17.6 g, 0.080 mol) and triethylamine (16.8 mL, 0.120 mol) are added. Stirring is continued for 16 h. The reaction mixture is filtered to remove triethylamine-HCl and the solvent is removed by rotary evaporation under high vacuum to give a thick oil. The oil is dissolved in 150 mL CH_2Cl_2 and applied to a silica gel column (150 g, 40 x 250 mm). The column is eluted with 3% methanol in CH_2Cl_2 to give the crude product as a solid. The crude solid is dissolved in 120 mL hot CH_2Cl_2 and cooled to -20 °C for 1 h. The resulting solid is filtered and washed with 50 mL CH_2Cl_2. The combined filtrates are evaporated to dryness. CH_2Cl_2 (40 mL) is added to this residue and the resulting slurry is stirred for 0.5 h at room temperature. The slurry is filtered and the solid washed with 25 mL CH_2Cl_2. The solids are combined to give 5.57 g of (3*S*, 6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-hydroxy-2*H*-azepin-2-one. 300 MHz ^{1}H NMR (DMSO) δ 7.42 (1 H, t, J = 5.1 Hz), 6.38 (1 H, d, J = 6.6 Hz), 4.60 (1 H, d, J = 4.2 Hz), 4.07 (1 H, m), 3.74 (1 H, m), 3.32 (1 H, m), 3.03 (1 H, m), 1.8-1.5 (4 H, m), 1.39 (9 H, s).

g) Preparation of (3*S*, 6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-*t*-butyl-dimethylsilyloxy-2*H*-azepin-2-one.

To a stirred solution of (3*S*, 6*R*)-3-(*tert*-butoxycarbonyl)aminohexahydro-6-hydroxy-2*H*-azepin-2-one (25 g, 102 mmol) in DMF (60 mL) is added *tert*-butyldimethylsilyl chloride (23.16 g, 153 mmol), and imidazole (10.45 g, 153 mmol). The reaction is stirred at room temperature for 18 h, diluted with 1 L of water and extracted with a 1:1 (2 x 200 mL) mixture of ethyl acetate and hexane. All organic layers are combined, washed with brine, dried with $NaSO_4$, and concentrated under vacuum. The residue is purified by recrystallization with ethyl acetate/hexane to give 28.5 g (78%) of (3*S*, 6*R*)-3-(*tert*-butoxycarbonyl) aminohexahydro-6-*tert*-butyldimethylsilyloxy-2*H*-azepin-2-one as a white solid, melting point: 65 – 66 °C; ^1H NMR ($CDCl_3$) δ 5.86 (d, J=6 Hz, 1H), 5.58 (t, J=6 Hz, 1H), 4.18 (m, 1H), 3.91 (s, 1H), 3.35(dd, J=6 Hz and 16 Hz, 1H), 3.07 (m, 1H), 1.80 (m, 4H), 1.40 (s, 9H), 0.83 (s, 9H), 0.004 (s, 6H).

h) Preparation of [(3S,6R)-6-(tert-butyl-dimethyl-silanyloxy)-2-oxo-1-pyridin-3-ylmethyl-azepan-3-yl]-carbamic acid tert-butyl ester

To a stirred solution of [(3S,6R)-6-(tert-butyl-dimethyl-silanyloxy)-2-oxo-azepan-3-yl]-carbamic acid tert-butyl ester (4.0 g, 11.1 mmol) in THF (30 mL) at –78 °C is added $KN(Si(CH_3)_3)_2$ (45.0 mL 1M THF, 45.0 mmol) slowly. The mixture is stirred at room temperature for 20 min, cooled to –78 °C, and 3-chloromethyl-pyridine hydrochloride (2.75 g, 16.7 mmol) is added in portions. The reaction is warmed to room temperature and stirred for 16 h, H_2O (20 mL) is added and the mixture is partitioned with H_2O/ether, the organic layer is separated, dried with Na_2SO_4 and evaporated to give a white solid, 5.0 g (quantitative) of [(3S,6R)-6-(tert-butyl-dimethyl-silanyloxy)-2-oxo-1-pyridin-3-ylmethyl-azepan-3-yl]-carbamic acid tert-butyl ester. MS (ESI) 899.3 $(2M+H)^+$

i) Preparation of (3S,6R)-3-amino-6-(tert-butyl-dimethyl-silanyloxy)-1-pyridin-3-ylmethyl-azepan-2-one

To a stirred solution of [(3S,6R)-6-(tert-butyl-dimethyl-silanyloxy)-2-oxo-1-pyridin-3-ylmethyl-azepan-3-yl]-carbamic acid tert-butyl ester (5.0 g, 11.1 mmol) in CH_2Cl_2 (50 mL) at –78 °C is added trimethylsilyl iodide (2.8 g, 14.0 mmol) neat. After 30 min the reaction solution is warmed to 0 °C and stirred for 15 min. The reaction is quenched with a solution of CH_3OH (25 mL) and NH_4HCO_3 (10 mL, saturated in H_2O), and partitioned with H_2O/CH_2Cl_2. The CH_2Cl_2 fraction is dried over Na_2SO_4 and evaporated to a gum and chromatographed on

silica (95% CH_2Cl_2 / 5% CH_3OH) to give 3.6 g (92.6%) of (3S,6R)-3-amino-6-(tert-butyl-dimethyl-silanyloxy)-1-pyridin-3-ylmethyl-azepan-2-one as a white solid. MS (ESI) 350.2 $(M+H)^+$

j) Preparation of (R)-N-[(3S,6R)-6-(tert-butyl-dimethyl-silanyloxy)-2-oxo-1-pyridin-3-ylmethyl-azepan-3-yl]-2-[(4R,5R,6R)-6-((E)-3,3-dimethyl-but-1-enyl)-5-hydroxy-2,2-dimethyl-[1,3]dioxan-4-yl]-2-methoxy-acetamide

A solution of (3S,6R)-3-amino-6-(tert-butyl-dimethyl-silanyloxy)-1-pyridin-3-ylmethyl-azepan-2-one (1.84 g, 5.3 mmol), (4R,4aR)-4-((E)-3,3-Dimethyl-but-1-enyl)-7-methoxy-2,2-dimethyl-tetrahydro-furo[3,2-d][1,3]dioxin-6-one (1.0 g, 3.5 mmol) and diisopropylethylamine (1.37 g, 11.0 mmol) in isopropanol (10 mL) is refluxed for 16 h. The solution is evaporated and chromatographed on silica (95% CH_2Cl_2 / 5% CH_3OH) to give 1.27 g (57.0%) of (R)-N-[(3S,6R)-6-(tert-butyl-dimethyl-silanyloxy)-2-oxo-1-pyridin-3-ylmethyl-azepan-3-yl]-2-[(4R,5R,6R)-6-((E)-3,3-dimethyl-but-1-enyl)-5-hydroxy-2,2-dimethyl-[1,3]dioxan-4-yl]-2-methoxy-acetamide as a white solid. MS (ESI) 634.3 $(M+H)^+$

Preparation of (R)-2-[(4R,5R,6R)-6-((E)-3,3-dimethyl-but-1-enyl)-5-hydroxy-2,2-dimethyl-[1,3]dioxan-4-yl]-N-((3S,6R)-6-hydroxy-2-oxo-1-pyridin-3-ylmethyl-azepan-3-yl)-2-methoxy-acetamide

To a stirred solution of (R)-N-[(3S,6R)-6-(tert-butyl-dimethyl-silanyloxy)-2-oxo-1-pyridin-3-ylmethyl-azepan-3-yl]-2-[(4R,5R,6R)-6-((E)-3,3-dimethyl-but-1-enyl)-5-hydroxy-2,2-dimethyl-[1,3]dioxan-4-yl]-2-methoxy-acetamide (1.2 g, 1.9 mmol) at room temperature is added tetrabutylammonium fluoride (5.68 mL, 1 M THF, 5.68 mmol). After 2 h, the solution is evaporated and chromatographed on silica (95% CH_2Cl_2 / 5% CH_3OH) to give 0.74 g (75.2 %) of (R)-2-[(4R,5R,6R)-6-((E)-3,3-dimethyl-but-1-enyl)-5-hydroxy-2,2-dimethyl-[1,3]dioxan-4-yl]-N-((3S,6R)-6-hydroxy-2-oxo-1-pyridin-3-ylmethyl-azepan-3-yl)-2-methoxy-acetamide as a white solid. ^1H NMR 300MHz δ 8.52(m, 2H), 7.69 (m, 1H), 7.29 (m, 1H), 5.77 (d, 1H), 5.54(dd, 1H), 4.69 (m, 2H), 4.29 (m, 2H), 4.10 (m, 2H), 3.92 (d, 1H), 3.54 (m, 2H), 3.50 (s, 3H), 3.33 (m,2H), 2.15 (m, 1H), 2.00 (m, 1H), 1.90 (m, 1H), 1.67 (m, 3H), 1.46 (m, 4H), 1.04 (s, 9H), 1.00 (t, 2H); MS (ESI) 520.2 $(M+H)^+$.

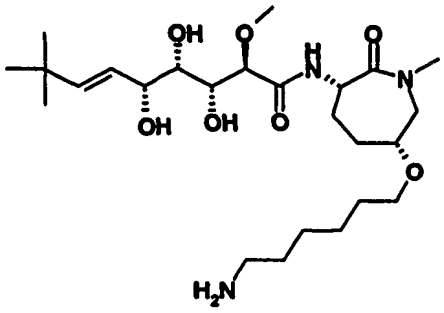
l) Preparation of tetradecanoic acid (3R,6S)-6-{(R)-2-[(4R,5R,6R)-6-((E)-3,3-dimethyl-but-1-enyl)-5-hydroxy-2,2-dimethyl-[1,3]dioxan-4-yl]-2-methoxy-acetylamino}-7-oxo-1-pyridin-3-ylmethyl-azepan-3-yl ester

To a stirred solution of tetradecanoic acid (0.39 g 1.7 mmol) and 4 dimethylaminopyridine (0.21 g, 1.7 mmol) in CH_2Cl_2 (15 mL) is added 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (0.34 g, 1.7 mmol) at room temperature. After 30 min (R)-2-[(4R,5R,6R)-6-((E)-3,3-dimethyl-but-1-enyl)-5-hydroxy-2,2-dimethyl-[1,3]dioxan-4-yl]-N-((3S,6R)-6-hydroxy-2-oxo-1-pyridin-3-ylmethyl-azepan-3-yl)-2-methoxy-acetamide (0.74 g, 1.4 mmol) is added and stirred for 16 h. The reaction is concentrated and chromatographed on silica (98% CH_2Cl_2 / 2% CH_3OH) to give 0.3 g (28.8 %) of tetradecanoic acid (3R,6S)-6-{(R)-2-[(4R,5R,6R)-6-((E)-3,3-dimethyl-but-1-enyl)-5-hydroxy-2,2-dimethyl-[1,3]dioxan-4-yl]-2-methoxy-acetylamino}-7-oxo-1-pyridin-3-ylmethyl-azepan-3-yl ester as a white solid. ^1H NMR 300MHz δ 8.54(s, 2H), 7.88 (d, 1H), 7.63 (d, 1H), 7.29 (m, 1H), 5.77 (d, 1H), 5.54(dd, 1H), 5.06 (d, 1H), 4.75 (m, 1H), 4.50 (m, 1H), 4.29 (m, 2H), 4.08 (d, 1H), 3.90 (d, 1H), 3.52 (s, 3H), 3.50 (m, 1H), 3.25 (d, 1H), 2.27 (t, 2H), 2.15 (m, 2H), 2.00 (m, 1H), 1.60 (m, 3H), 1.46 (d, 2H), 1.25 (m, 24H), 1.04 (s, 9H), 0.88 (t, 3H); MS (ESI) 730.3 $(M+H)^+$.

m) Preparation of title compound tetradecanoic acid (3R,6S)-7-oxo-1-pyridin-3-ylmethyl-6-((2R,3R,4S,5R)-(E)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-non-6-enoylamino)-azepan-3-yl ester

To a solution of TFA/THF/H_2O (3/3/2) (30 mL) at 0 °C is added tetradecanoic acid (3R,6S)-6-{(R)-2-[(4R,5R,6R)-6-((E)-3,3-dimethyl-but-1-enyl)-5-hydroxy-2,2-dimethyl-[1,3]dioxan-4-yl]-2-methoxy-acetylamino}-7-oxo-1-pyridin-3-ylmethyl-azepan-3-yl ester (0.3 g, 0.42 mmol). After 30 min the reaction is evaporated under high vacuum, toluene is added (20 mL) and evaporated under high vacuum to remove remaining TFA. The residue is dissolved in CH_2Cl_2 at 0 °C and neutralized by adding NH_4OH dropwise. The solution is concentrated and chromatographed on silica (98% CH_2Cl_2 / 2% CH_3OH) to give 0.2 g (70.7 %) of tetradecanoic acid (3R,6S)-7-oxo-1-pyridin-3-ylmethyl-6-((2R,3R,4S,5R)-(E)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-non-6-enoylamino)-azepan-3-yl ester as a with solid. ^1H NMR 300MHz δ 8.62 (s, 2H), 8.17 (d, 1H), 7.67 (d, 1H), 7.33 (m, 1H), 5.83 (d, 1H), 5.42(dd, 1H), 4.69 (m, 1H), 4.54 (m, 1H), 4.33 (d, 1H), 4.32 (t, 1H), 3.83 (dd, 2H), 3.67 (d, 1H), 3.25 (s, 3H), 3.17 (m, 1H), 2.94 (d, 1H), 2.29 (t, 2H), 2.13 (m, 2H), 2.00 (m, 1H), 1.60 (m, 3H), 1.29 (m, 24H), 1.04 (s, 9H), 0.89 (t, 3H); MS (ESI) 690.3 $(M+H)^+$.

EXAMPLE 2: (E)-(2R,3R,4S,5R)-3,4,5-Trihydroxy-2-methoxy-8,8-dimethyl-non-6-enoic acid [(3S,6R)-6-(6-amino-hexyloxy)-1-methyl-2-oxo-azepan-3-yl]-amide



a) Preparation of [(3S,6R)-6-(tert-butyl-dimethyl-silanyloxy)-1-methyl-2-oxo-azepan-3-yl]-carbamic acid tert-butyl ester

Following the procedure of Example 1(f)-1(h), except CH_3-I is substituted for 2-chloromethyl-pyridine and one equivalent of $KN(Si(CH_3)_3)_2$ is used in step 1(h) to give the product as an oil. ^1H NMR ($CDCl_3$) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 1.44 (s, 9H), 1.8 (m, 4H), 3.06 (s, 3H), 3.2 (dd, 1H), 3.7 (d, 1H), 4.0 (m, 1H). 4.28 (dd, 1H), 6.0 (d, 1H).

b) Preparation of ((3S,6R)-6-hydroxy-1-methyl-2-oxo-azepan-3-yl)-carbamic acid tert-butyl ester

To a solution of [(3S,6R)-6-(tert-butyl-dimethyl-silanyloxy)-1-methyl-2-oxo-azepan-3-yl]-carbamic acid tert-butyl ester (0.85 g, 2.27 mmol) in THF (40 mL) is added tetrabutylammonium fluoride (3 mL 1M THF, 3 mmol) at room temperature. The reaction solution is stirred for 4 h, then H_2O (40 mL) is added and the solution concentrated under vacuum to ½ its volume and extracted 3x with CH_2Cl_2 (40 mL). The combined CH_2Cl_2 extracts are adsorbed on silica and chromatographed (5% CH_3OH/ CH_2Cl_2) to give 0.568 g (72%) of ((3S,6R)-6-hydroxy-1-methyl-2-oxo-azepan-3-yl)-carbamic acid tert-butyl ester as a white solid. ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.7-2.05 (m, 4H), 3.1 (s, 3H), 3.37 (dd, 1H), 3.73 (d, 1H), 4.07 (m, 1H), 4.31 (m, 1H), 6.0 (d, 1H).

Preparation of [(3S,6R)-6-(6-azido-hexyloxy)-1-methyl-2-oxo-azepan-3-yl]-carbamic acid tert-butyl ester

To a stirred solution of ((3S,6R)-6-hydroxy-1-methyl-2-oxo-azepan-3-yl)-carbamic acid tert-butyl ester (0.70 g, 2.6 mmol) in THF (5 mL) cooled to –78 °C is added $NaN(Si(CH_3)_3)_2$ (2.8 mL 1M THF, 2.8 mmol). After 10 min trifluoro-methanesulfonic acid 6-azido-hexyl ester (0.76

g, 3.1 mmol) is added neat and stirred for 10 min at –78 °C then warmed and stirred at room temperature for 1 h. $NaHCO_3$ (5 mL 1M H_2O) is added and the solution is partitioned with H_2O/EtOAc, the EtOAc extract is dried with Na_2SO_4 and evaporated to an oil. The oil is adsorbed on silica and chromatographed (20% EtOAc/ CH_2Cl_2) to give 0.32 g (32%) of [(3S,6R)-6-(6-azido-hexyloxy)-1-methyl-2-oxo-azepan-3-yl]-carbamic acid tert-butyl ester as an oil. ^1H NMR ($CDCl_3$) δ 1.34 (s, 9H), 1.24-2.1 (m, 12H), 2.95 (s, 3H), 3.1-3.35 (m, 6H), 3.44 (m, 1H), 3.55 (d, 1H), 4.2 (m, 1H).

Preparation of (3S,6R)-3-amino-6-(6-azido-hexyloxy)-1-methyl-azepan-2-one
To a stirred solution of [(3S,6R)-6-(6-azido-hexyloxy)-1-methyl-2-oxo-azepan-3-yl]-carbamic acid tert-butyl ester (0.32 g, 0.83 mmol) in CH_2Cl_2 (4 mL) is added TFA (1 mL) at room temperature. After 1 h, the reaction is evaporated under vacuum, toluene (20 mL) is added and evaporated under vacuum to remove remaining TFA. The residue is dissolved in CH_2Cl_2 (20 mL) saturated with NH_3 adsorbed on silica and chromatographed (50% EtOAc/CH_2Cl_2/NH_3 then 10% CH_3OH/CH_2Cl_2/NH_3) to give 0.207 g (88%) of (3S,6R)-3-amino-6-(6-azido-hexyloxy)-1-methyl-azepan-2-one as an oil. MS (ESI) 284.2 $(M+H)^+$

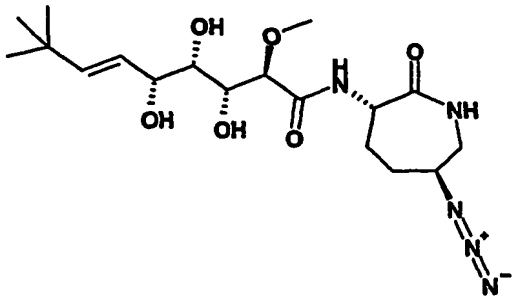
Preparation of (R)-N-[(3S,6R)-6-(6-azido-hexyloxy)-1-methyl-2-oxo-azepan-3-yl]-2-[(4R,5R,6R)-6-((E)-3,3-dimethyl-but-1-enyl)-5-hydroxy-2,2-dimethyl-[1,3]dioxan-4-yl]-2-methoxy-acetamide
To a solution of (3S,6R)-3-amino-6-(6-azido-hexyloxy)-1-methyl-azepan-2-one (0.207 g, 0.73 mmol) in isopropanol (1 mL) is added (4R,4aR)-4-((E)-3,3-dimethyl-but-1-enyl)-7-methoxy-2,2-dimethyl-tetrahydro-furo[3,2-d][1,3]dioxin-6-one (0.3 g, 1 mmol) and heated to reflux for 18 h. The solution is evaporated under vacuum adsorbed on silica and chromatographed (CH_2Cl_2 to EtOAc gradient) to give 0.245 g (59%) of (R)-N-[(3S,6R)-6-(6-azido-hexyloxy)-1-methyl-2-oxo-azepan-3-yl]-2-[(4R,5R,6R)-6-((E)-3,3-dimethyl-but-1-enyl)-5-hydroxy-2,2-dimethyl-[1,3]dioxan-4-yl]-2-methoxy-acetamide as a solid. (ESI) 568.1 $(M+H)^+$

f) Preparation of (E)-(2R,3R,4S,5R)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-non-6-enoic acid [(3S,6R)-6-(6-azido-hexyloxy)-1-methyl-2-oxo-azepan-3-yl]-amide
Following the procedure of Example 1 m) except (R)-N-[(3S,6R)-6-(6-azido-hexyloxy)-1-methyl-2-oxo-azepan-3-yl]-2-[(4R,5R,6R)-6-((E)-3,3-dimethyl-but-1-enyl)-5-hydroxy-2,2-dimethyl-[1,3]dioxan-4-yl]-2-methoxy-acetamide is substituted for tetradecanoic acid

(3R,6S)-6-{(R)-2-[(4R,5R,6R)-6-((E)-3,3-dimethyl-but-1-enyl)-5-hydroxy-2,2-dimethyl-[1,3]dioxan-4-yl]-2-methoxy-acetylamino}-7-oxo-1-pyridin-3-ylmethyl-azepan-3-yl ester.
MS (ESI) 528.0 $(M+H)^+$

g) Preparation of title compound (E)-(2R,3R,4S,5R)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-non-6-enoic acid [(3S,6R)-6-(6-amino-hexyloxy)-1-methyl-2-oxo-azepan-3-yl]-amide
To a stirred solution of (E)-(2R,3R,4S,5R)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-non-6-enoic acid [(3S,6R)-6-(6-azido-hexyloxy)-1-methyl-2-oxo-azepan-3-yl]-amide (0.13 g, 0.25 mmol) in THF (2 mL) is added H_2O and triphenylphosphine (0.120 g, 0.5 mmol). After 8 h the reaction solution is evaporated under vacuum to give a semisolid residue that is dissolved in CH_2Cl_2 (10 mL), adsorbed on silica and chromatographed (CH_2Cl_2/NH_3 to 25% $CH_3OH/CH_2Cl_2/NH_3$ gradient) to give 0.106 g (85%) of (E)-(2R,3R,4S,5R)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-non-6-enoic acid [(3S,6R)-6-(6-amino-hexyloxy)-1-methyl-2-oxo-azepan-3-yl]-amide as a white solid. MS (ESI) 502.1 $(M+H)^+$

EXAMPLE 3: (E)-(2R,3R,4S,5R)-3,4,5-Trihydroxy-2-methoxy-8,8-dimethyl-non-6-enoic acid ((3S,6S)-6-azido-2-oxo-azepan-3-yl)-amide



Preparation of ((3S,6S)-6-azido-2-oxo-azepan-3-yl)-carbamic acid tert-butyl ester
To a stirred solution of ((3S,6R)-6-hydroxy-2-oxo-azepan-3-yl)-carbamic acid tert-butyl ester (3 g, 12.3 mmol example 1 f) and triphenylphosphine (3.75 g, 14.1 mmol) in THF (200 mL) at 0°C is added diethyl azodicarboxylate (2.2 mL, 13.5 mmol) at a rate to maintain a temperature <5 °C followed immediately by addition of diphenylphosphoryl azide (2.9 mL, 13.5 mmol). The reaction is stirred for 60 h at room temperature in the dark, the solvent is removed under vacuum and the residue chromatographed on silica (hexane to ether

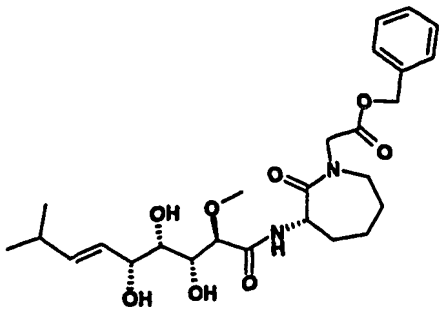
gradient) to give 2.33 g (70%) of ((3S,6S)-6-azido-2-oxo-azepan-3-yl)-carbamic acid tert-butyl ester as a solid. MS (ESI) 270 $(M+H)^+$

Preparation of (3S,6S)-3-amino-6-azido-azepan-2-one
Following the procedure of example 2 d) ((3S,6S)-6-azido-2-oxo-azepan-3-yl)-carbamic acid tert-butyl ester is substituted for [(3S,6R)-6-(6-azido-hexyloxy)-1-methyl-2-oxo-azepan-3-yl]-carbamic acid tert-butyl ester to give (3S,6S)-3-amino-6-azido-azepan-2-one. MS (ESI) 170 $(M+H)^+$

Preparation of (R)-N-((3S,6S)-6-azido-2-oxo-azepan-3-yl)-2-[(4R,5R,6R)-6-((E)-3,3-dimethyl-but-1-enyl)-5-hydroxy-2,2-dimethyl-[1,3]dioxan-4-yl]-2-methoxy-acetamide
Following the procedure of example 2 e) (3S,6S)-3-amino-6-azido-azepan-2-one is substituted for (3S,6R)-3-amino-6-(6-azido-hexyloxy)-1-methyl-azepan-2-one to give (R)-N-((3S,6S)-6-azido-2-oxo-azepan-3-yl)-2-[(4R,5R,6R)-6-((E)-3,3-dimethyl-but-1-enyl)-5-hydroxy-2,2-dimethyl-[1,3]dioxan-4-yl]-2-methoxy-acetamide. MS (ESI) 454.2 $(M+H)^+$

d) Preparation of title compound (E)-(2R,3R,4S,5R)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-non-6-enoic acid ((3S,6S)-6-azido-2-oxo-azepan-3-yl)-amide
Following the procedure of example 1 m) (R)-N-((3S,6S)-6-azido-2-oxo-azepan-3-yl)-2-[(4R,5R,6R)-6-((E)-3,3-dimethyl-but-1-enyl)-5-hydroxy-2,2-dimethyl-[1,3]dioxan-4-yl]-2-methoxy-acetamide is substituted for tetradecanoic acid (3R,6S)-6-{(R)-2-[(4R,5R,6R)-6-((E)-3,3-dimethyl-but-1-enyl)-5-hydroxy-2,2-dimethyl-[1,3]dioxan-4-yl]-2-methoxy-acetylamino}-7-oxo-1-pyridin-3-ylmethyl-azepan-3-yl ester to give the title compound. MS (ESI) 414.2 $(M+H)^+$

EXAMPLE 4: [(S)-2-Oxo-3-((2R,3R,4S,5R)-(E)-3,4,5-trihydroxy-2-methoxy-8-methyl-non-6-enoylamino)-azepan-1-yl]-acetic acid benzyl ester



Preparation of (4R,4aR)-7-methoxy-2,2-dimethyl-4-((E)-3-methyl-but-1-enyl)-tetrahydro-furo[3,2-d][1,3]dioxin-6-one

Following the procedure of example 1 a) - e) except 1,1-diiodo-2-methyl-propane is substituted for 1,1-diiodo-2,2-dimethyl-propane to give (4R,4aR)-7-methoxy-2,2-dimethyl-4-((E)-3-methyl-but-1-enyl)-tetrahydro-furo[3,2-d][1,3]dioxin-6-one as a white solid. ^{1}HNMR ($CDCl_3$) δ 5.85 (dd, J=15.6, 6.22 Hz, 1H), 5.64 (ddd, J= 15.6, 7.5, 1.27 Hz, 1H), 4.74 (dd, J= 3.79, 2.09 Hz, 1H), 4.48 (dd, J= 7.49, 1.78 Hz, 1H), 4.12 (d, J= 3.86 Hx, 1H), 4.02 (t, J= 2.02 Hz, 1H), 3.68 (s, 3H), 2.36 (m, 1H), 1.56 (s, 3H), 1.51 (s, 3H), 1.04 (d, J= 1.9 Hz, 3H), 1.03 (d, J= 1.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.8, 143.2, 122.0, 98.7, 79.0, 71.7, 70.0, 67.6, 59.2, 30.7, 29.2, 21.9, 21.8, 19.2. HRMS: calculated for $(M+Na)^+$ ($C_{14}H_{22}O_6Na$) 293.1365, found 293.1355.

Preparation of ((S)-3-amino-2-oxo-azepan-1-yl)-acetic acid benzyl ester

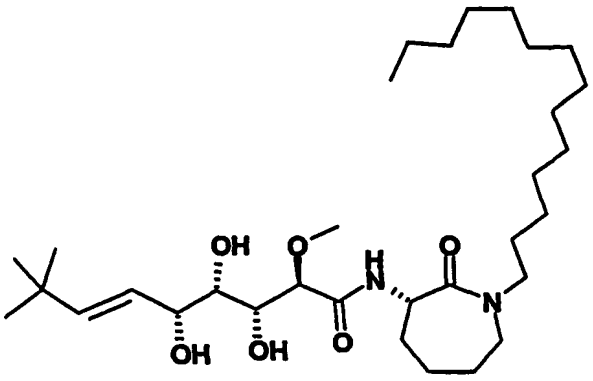
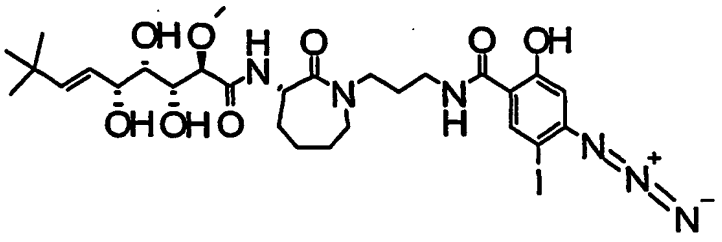
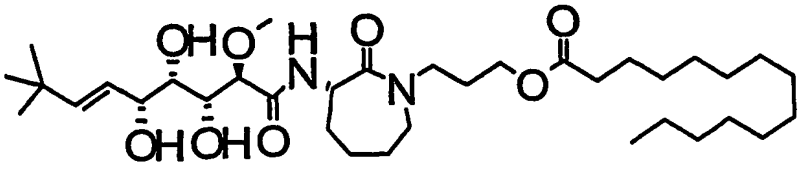
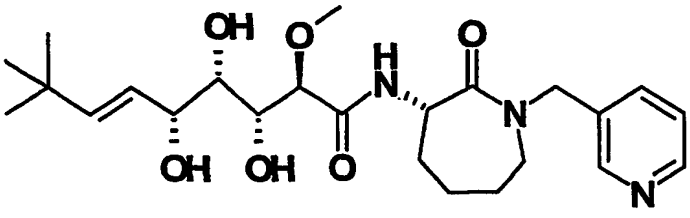
Following the procedure of example 1 h) except ((S)-2-oxo-azepan-3-yl)-carbamic acid tert-butyl ester is substituted for [(3S,6R)-6-(tert-butyl-dimethyl-silanyloxy)-2-oxo-azepan-3-yl]-carbamic acid tert-butyl ester and bromo-acetic acid benzyl ester is substituted for 2-chloromethyl-pyridine and one equivalent of $KN(Si(CH_3)_3)_2$ base to give ((S)-3-tert-butoxycarbonylamino-2-oxo-azepan-1-yl)-acetic acid benzyl ester. Removal of the Boc group by procedure 2 d) gives ((S)-3-amino-2-oxo-azepan-1-yl)-acetic acid benzyl ester.

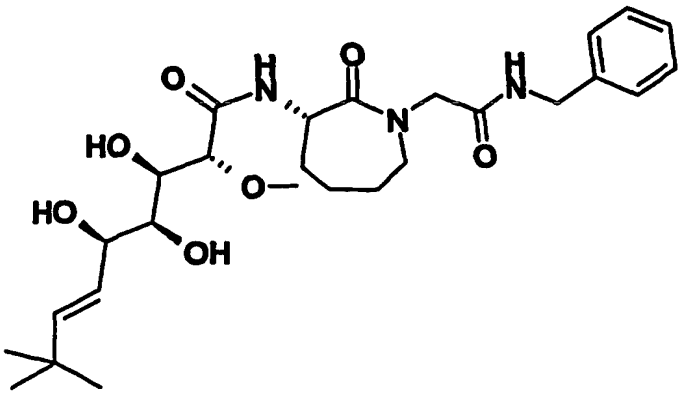
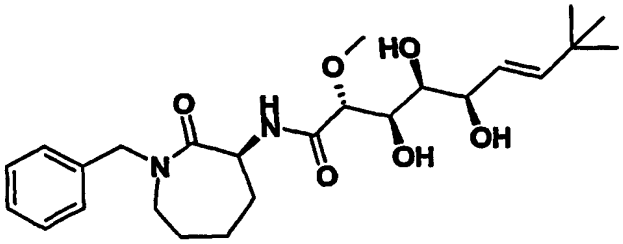
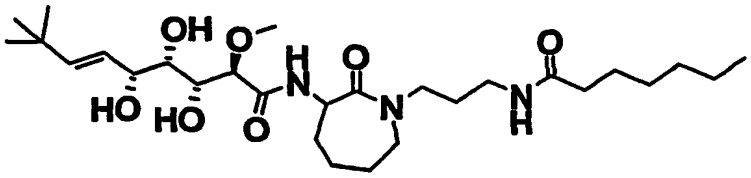
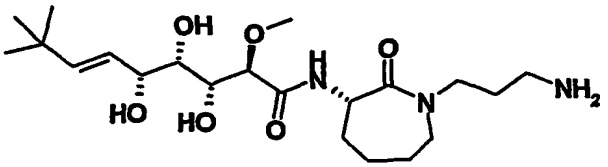
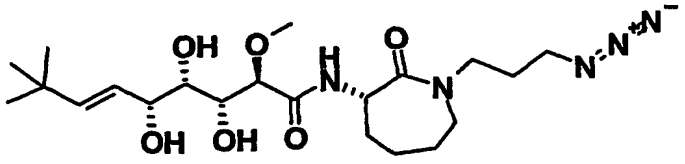
c) Preparation of title compound [(S)-2-oxo-3-((2R,3R,4S,5R)-(E)-3,4,5-trihydroxy-2-methoxy-8-methyl-non-6-enoylamino)-azepan-1-yl]-acetic acid benzyl ester

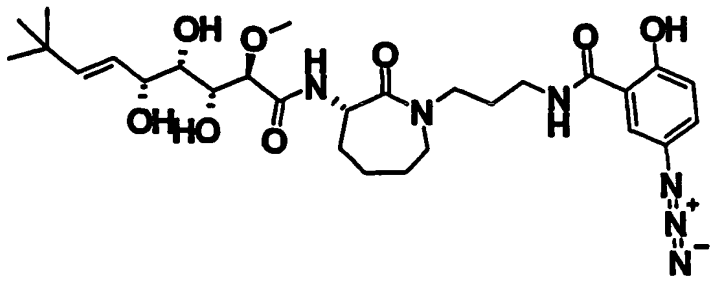
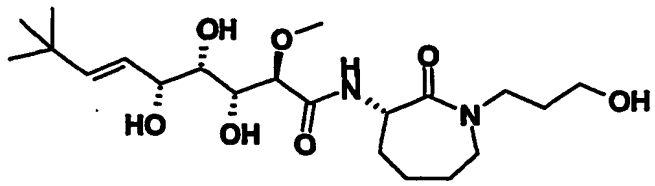
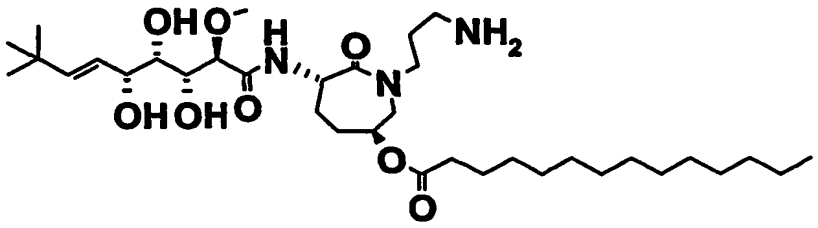
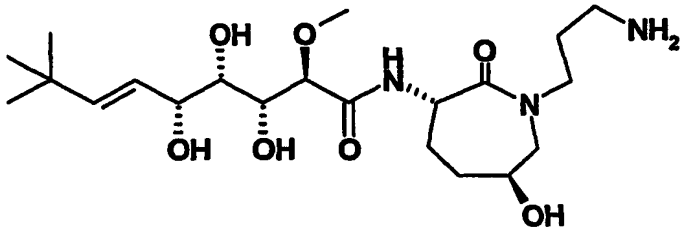
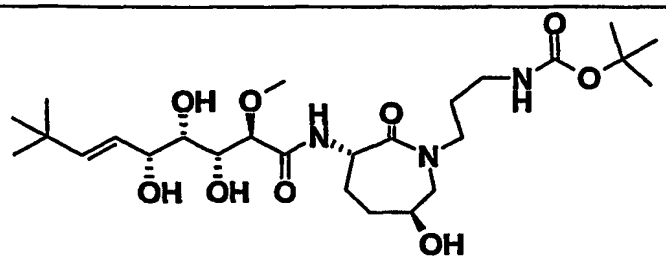
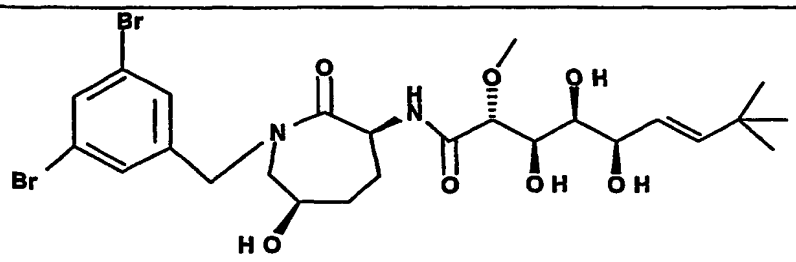
The product of 4 b) is processed as in example 2 e) – f) to give the title compound as a white solid.

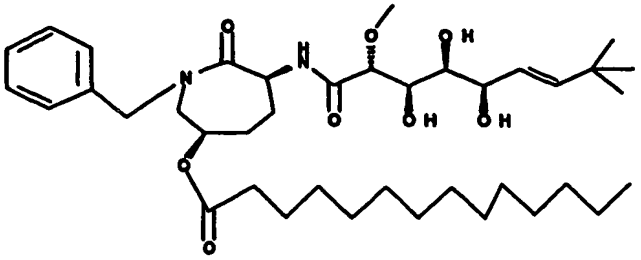
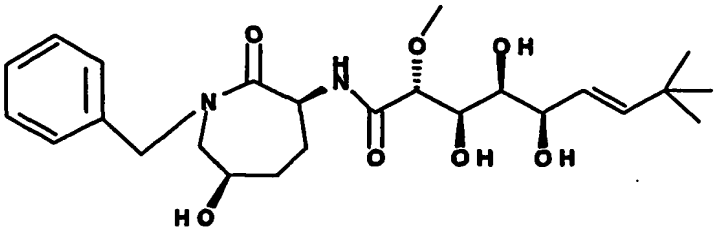
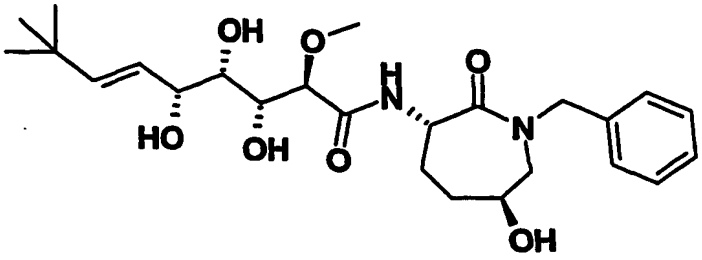
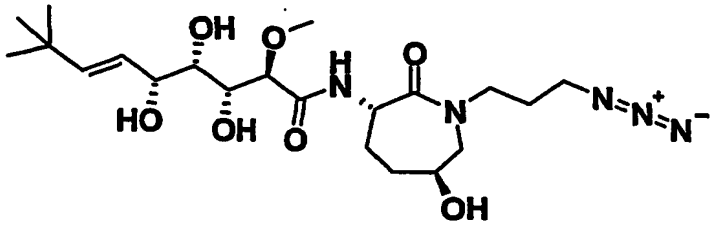
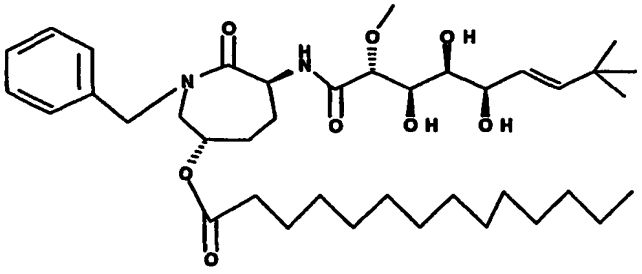
Examples 5-59

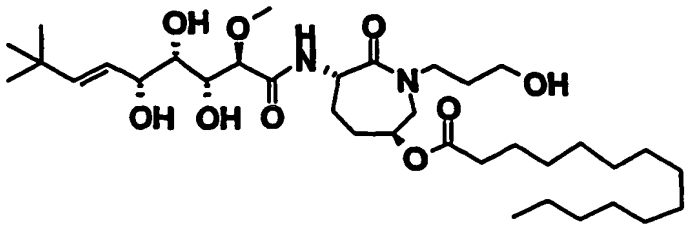
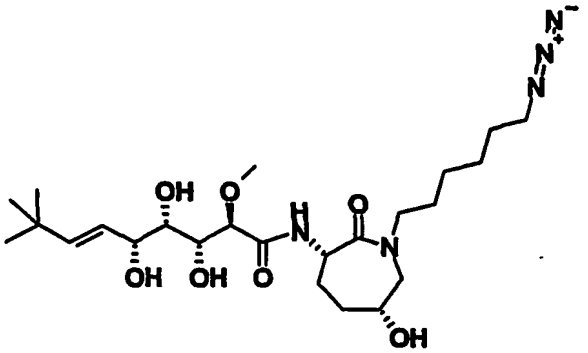
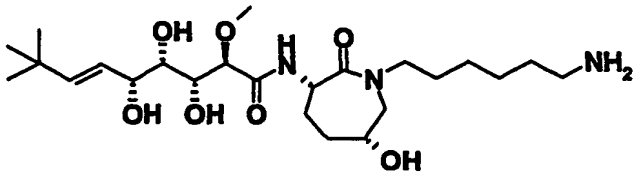
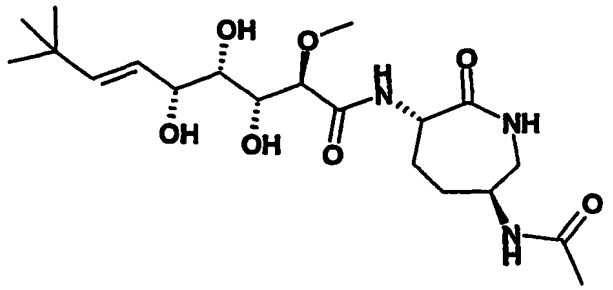
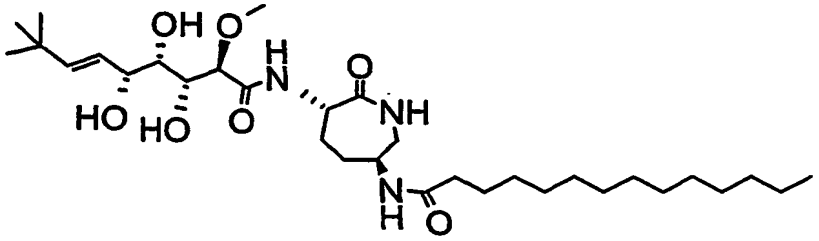
The following compounds are prepared by similar methods utilizing analogous starting materials:

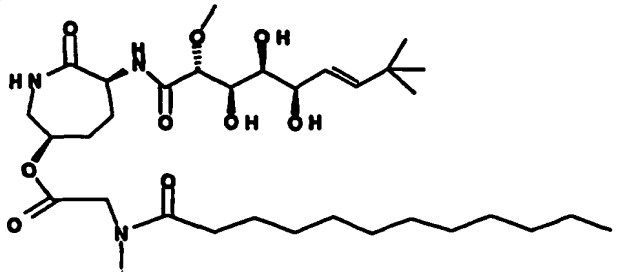
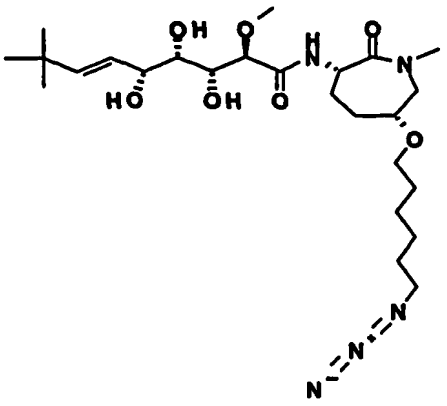
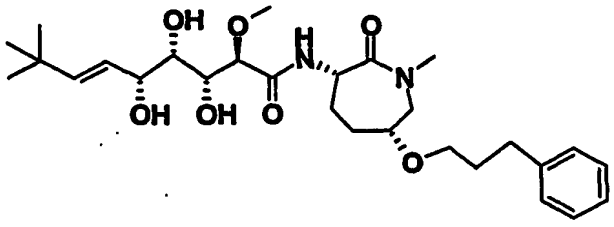
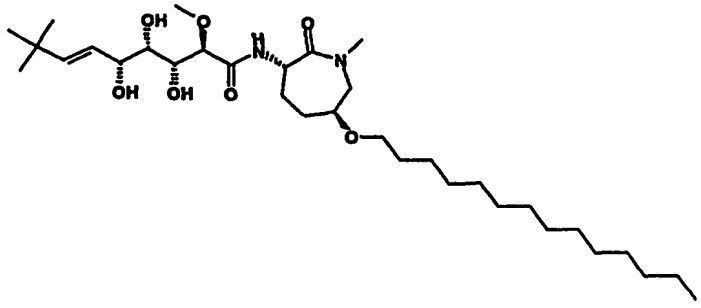
	Example 5 MS ESI 569.3 $(M+H)^+$
	Example 6 MS ESI 717.2 $(M+H)^+$
	Example 7 MS ESI 641.5 $(M+H)^+$
	Example 8 MS ESI 464.4 $(M+H)^+$

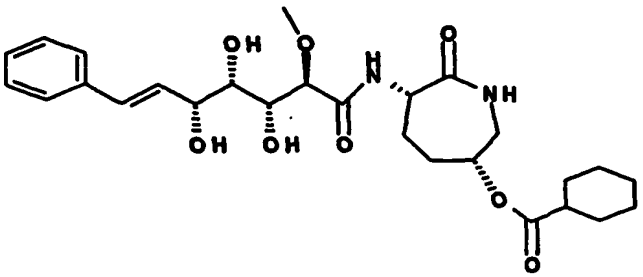
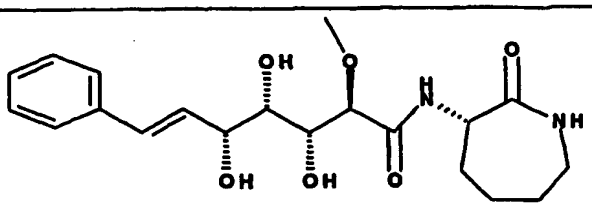
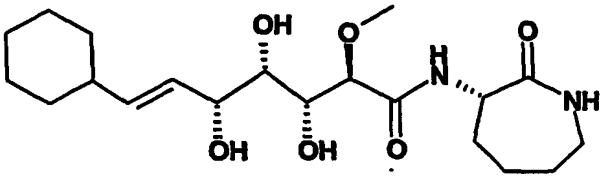
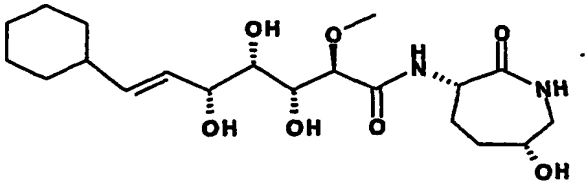
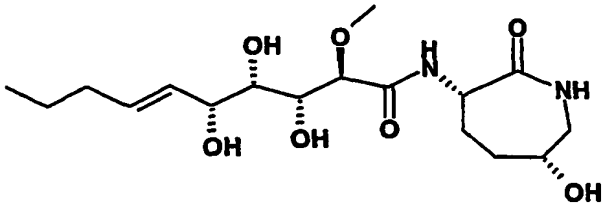
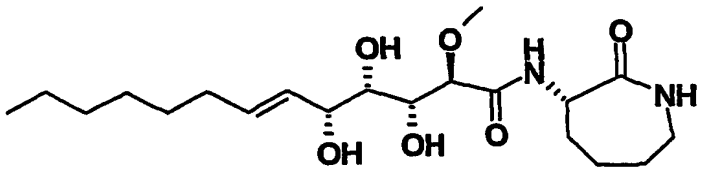
	Example 9 MS ESI 542.3 $(M+Na)^+$
	Example 10 MS ESI 463.3 $(M+H)^+$
	Example 11 MS ESI 542.3 $(M+H)^+$
	Example 12 MS ESI 430.2 $(M+H)^+$
	Example 13 MS ESI 472.3 $(M+H)^+$

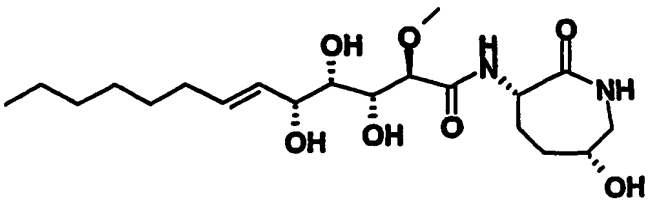
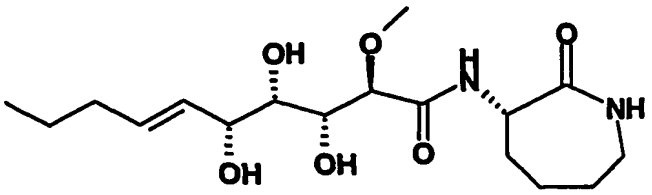
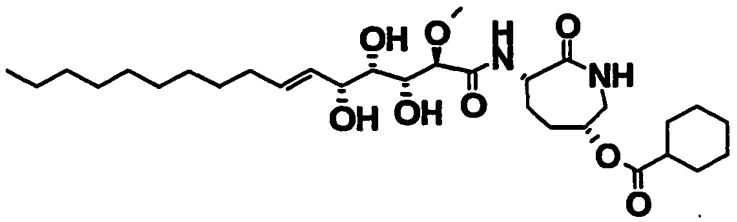
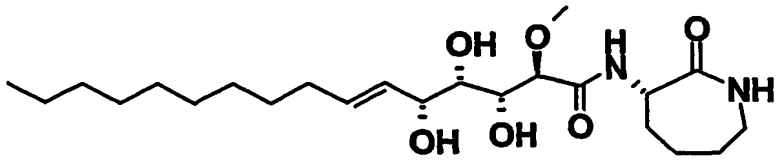
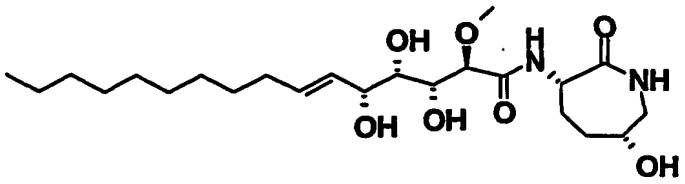
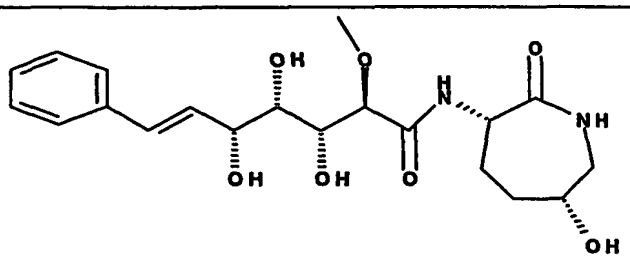
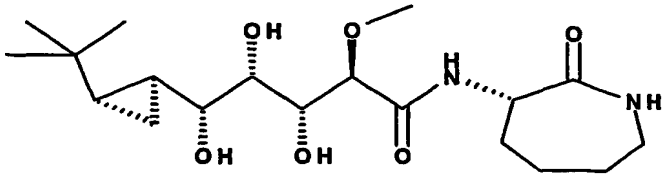
	Example 14 MS ESI 591.2 $(M+H)^+$
	Example 15 MS ESI 431.2 $(M+H)^+$
	Example 16 MS ESI 656.4 $(M+H)^+$
	Example 17 MS ESI 446.2 $(M+H)^+$
	Example 18 MS ESI 546.3 $(M+H)^+$
	Example 19 MS ESI 637.1 $(M+H)^+$

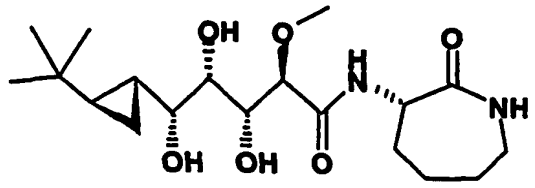
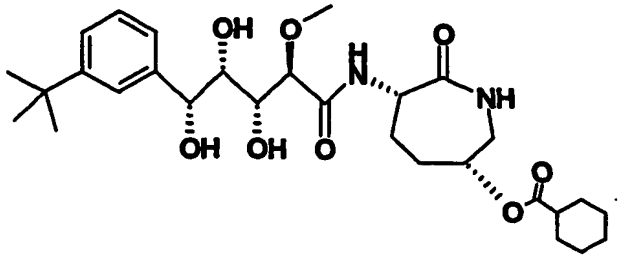
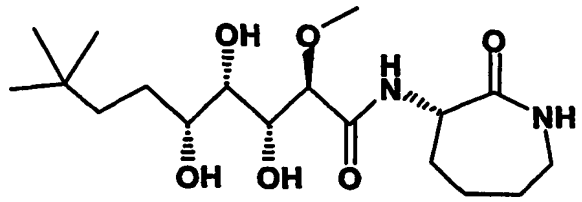
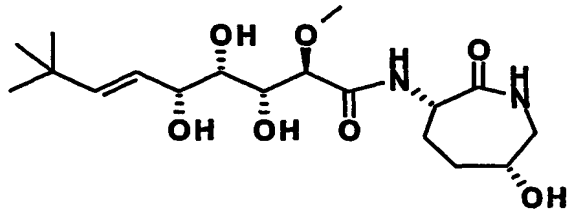
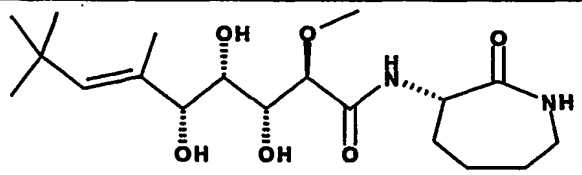
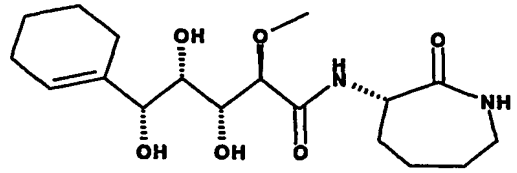
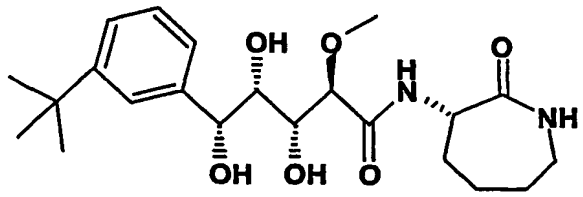
	Example 20 MS ESI 689.4 $(M+H)^+$
	Example 21 MS ESI 479.2 $(M+H)^+$
	Example 22 MS ESI 479.2 $(M+H)^+$
	Example 23 MS ESI 472.2 $(M+H)^+$
	Example 24 MS ESI 689.2 $(M+H)^+$

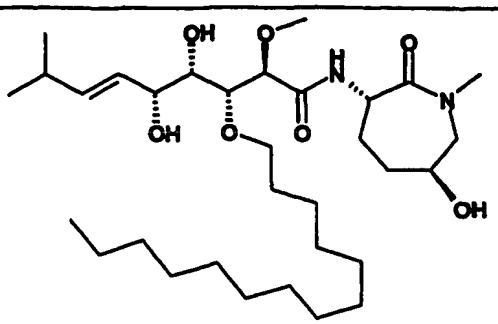
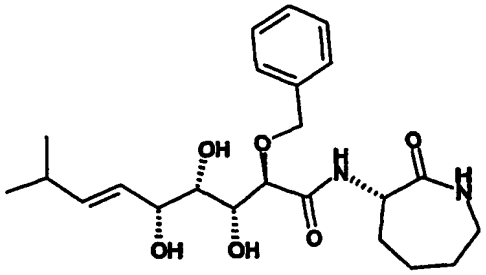
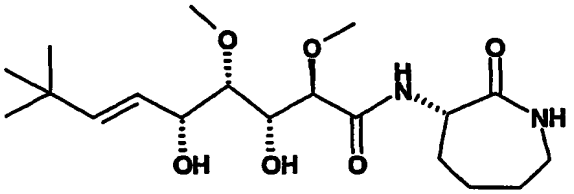
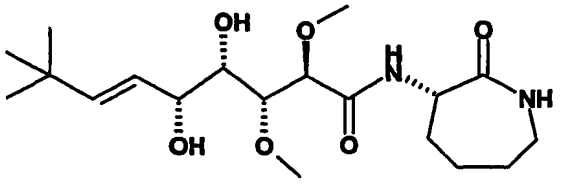
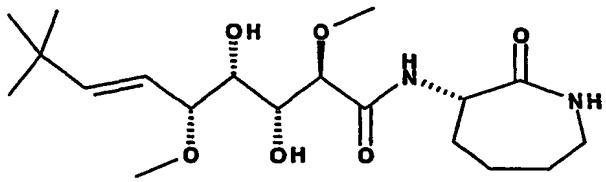
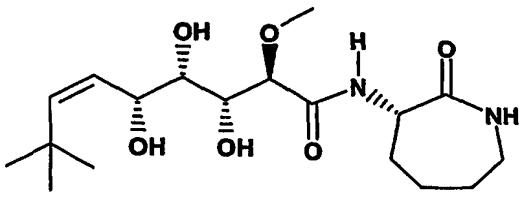
	Example 25 MS ESI 657.3 $(M+H)^+$
	Example 26 MS ESI 514.1 $(M+H)^+$
	Example 27 MS ESI 488.1 $(M+H)^+$
	Example 28 MS ESI 430.2 $(M+H)^+$
	Example 29 MS ESI 598.2 $(M+H)^+$

	Example 30 MS ESI 642.3 $(M+H)^+$
	Example 31 MS ESI 528.0 $(M+H)^+$
	Example 32 MS ESI 521.2 $(M+H)^+$
	Example 33 MS ESI 1197.4 $(2M+H)^+$

	Example 34 MS ESI 519.0 $(M+H)^+$
	Example 35 MS ESI 393.0 $(M+H)^+$
	Example 36 MS ESI 398.5 (M+H)+
	Example 37
	Example 38 MS ESI 375.1 $(M+H)^+$
	Example 39 MS ESI 401.21 $(M+H)^+$

	Example 40 MS ESI 417.1 $(M+H)^+$
	Example 41 MS ESI 359.3 $(M+H)^+$
	Example 42 MS ESI 569.5 $(M+H)^+$
	Example 43 MS ESI 443.4 $(M+H)^+$
	Example 44 MS ESI 459.4 $(M+H)^+$
	Example 45 MS ESI 409.3 $(M+H)^+$
	Example 46 MS ESI 387.3 $(M+H)^+$

	Example 47 MS ESI 387.3 $(M+H)^+$
	Example 48 MS ESI 549.3 $(M+H)^+$
	Example 49 MS ESI 375.3 $(M+H)^+$
	Example 50 MS ESI $(M+H)^+$
	Example 51 MS ESI 387.3 $(M+H)^+$
	Example 52 MS ESI 371.2 $(M+H)^+$
	Example 53 MS ESI 423.2 $(M+H)^+$

	Example 54 MS ESI 585.4 $(M+H)^+$
	Example 55 MS ESI 435.0 $(M+H)^+$
	Example 56 MS ESI 387.2 $(M+H)^+$
	Example 57 MS ESI 387.3 $(M+H)^+$
	Example 58 MS ESI 387.2 $(M+H)^+$
	Example 59

The anti-tumor activity of the compounds of formula I may be demonstrated employing the Anchorage Dependent Growth Monolayer Assay (ADGMA) which measures the growth inhibitory effects of test compounds on proliferation of adherent cell monolayers. This assay was adapted from the 60 cell line assay used by the National Cancer Institute (NCI) with the following modifications: 1) cell lines representative for the important tumor types, for example, MDA-MB-435 breast and A549 non-small cell lung, are utilized; and 2) a tetrazolium derivative, *viz.*, MTS, is utilized to determine cell density.

The ADGMA compares the number of viable cells following a 3-day exposure to a test compound relative to a number of cells present at the time the test compound is added. Cell viability is measured using a tetrazolium derivative, *viz.*, 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt (MTS) that is metabolically reduced in the presence of an electron coupling agent (PMS; phenazine methosulfate) by viable cells to a water-soluble formazan derivative. The absorbance at 490 nm (A_{490}) of the formazan derivative is proportional to the number of viable cells. The IC_{50} for a test compound is the concentration of compound required to reduce the final cell number to 50% of the final control cell number.

The MDA-MB-435 breast carcinoma line is obtained from the American Type Culture Collection (ATCC) and used between passages 4-20 following thawing. MDA-MB-435 breast carcinoma is maintained and plated in DME/F12 medium containing 10% fetal bovine serum, 15 mM HEPES (pH=7.4), penicillin 100 units/mL, and streptomycin 100 micrograms/mL.

The A549 non-small cell lung lines are obtained from the American Type Culture Collection (ATCC) and used between passages 4-20 following thawing. A549 cells are maintained in RPMI 1640 containing 5% FBS, 5 mg/mL insulin, 5 mg/mL transferring, 5 mg/mL selenous acid, 1 nM β- estradiol, 1 nM testosterone, 100 units/mL penicillin and 100 ug/mL streptomycin.

Cell lines are trypsinized and counted using a Coulter counter to determine plating densities. Cells are then plated in their respective maintenance media (100 µL/well) in 96 well plates at the following densities: MDA-MB-435, 3,000 cells/well; A549, 700 cells/well. The number of cells plates as determined in preliminary experiments, results in cell densities of 75-90% of

confluency by 4 days after plating. Initial cell densities, assayed one day after plating, are roughly 0.15-0.20 absorbance units greater than the media blank. Ninety-six well plates are seeded on day 0 and the test compounds are added on day 1. A control plate is created for each cell line that receives media only in row A and cells in row B. One day following plating, test compounds are added (in a final volume of 100 µL) to the test plates. Control plates receive 10 µL MTS mixture (prepared fresh on day of addition to cell plates at a ratio of 10 µL of a 0.92 mg/mL solution of PMS to a 190 µL of a 2 mg/mL solution of MTS) and 100 µL media. A_{490} of control plates is read 4 h after MTS addition to determine initial cell density values for each cell line. Three days after addition of the test compound, 10 µL/well of MTS mixture is added to the test plates and A_{490} is read 4 h later. A_{490} values for wells containing cells are corrected for media absorbance, then normalized to initial density readings to determine percent net growth. IC_{50} values are determined from graphs of percent net growth as a function of compound concentration. Percent net growth is calculated as (Cell + Drug A_{490} – Initial A_{490}/Cell + Drug Vehicle A_{490} – Initial A_{490}).

Each of the compounds of Examples 1-59 shows an IC_{50} value in the range from 0.001 µM to 100 µM in the ADGMA with at least one carcinoma cell line.